Intramolecular [4+2] Cycloaddition Reactions:

Influence of Ring Size on endo/exo Ratios

by

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Abstract

Natural products have contributed to health care and prevention of diseases for thousands of years. One family of bioactive compounds that is of particular interest to the MaGee group is the manzamine alkaloids and their derivatives. During their studies on the synthesis of the ABC-tricyclic core targeted for manzamine A and B, an intramolecular Diels-Alder reaction was used that resulted in a 25:1 ratio of endo to exo selectivity. This contrasted other results where a similar substrate resulted in a 2:1 ratio of endo to exo stereoisomers.

Therefore a study was initiated to look at the influence of the ring size, where the dienophile is contained, on endo/exo ratio’s in the intramolecular Diels-Alder reaction. The intramolecular Diels-Alder reaction was examined where the dienophile was embedded in 5, 7, 9 and 11-membered C-rings. While the 5- and 7-membered keto-acids were known compounds, synthetic routes had to be designed to make the other homologues. Once these were made and coupled with dieneamine, it was discovered that depending on ring size different endo/exo ratio’s were obtained. The five and seven-membered C-rings produced a ratio of 2:1 endo:exo, in contrast to the nine-membered C-ring, which produced an 18:1 endo:exo. The eleven-membered C-ring produced a ratio of only 5.4:1 endo:exo. Although the exact reasons for the differences are not completely known, it is clear that the conformational flexibility of the rings plays a major role.
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Table of Contents

Abstract .............................................................................................................................. II

Acknowledgements ........................................................................................................ III

Table of Contents .......................................................................................................... IV

List of Tables, Scheme and Figures ................................................................................ VI

List of Symbols and Abbreviations ............................................................................... X

Introduction .................................................................................................................... 1

I.1. Background information on the manzamine alkaloids ........................................... 1

I.2. General remarks about pericyclic reactions ......................................................... 6

I.2.1. Pericyclic Diels-Alder reactions ........................................................................ 7

I.2.2. Possible mechanisms and molecular orbital theory of Diels-Alder reactions . 8

I.2.3. Reactivity of Diels-Alder reaction ..................................................................... 10

I.2.4. Regioselectivity of Diels-Alder reactions ......................................................... 12

I.2.5. Stereochemistry of the Diels-Alder reaction ..................................................... 14

I.3. Primary objective of the study .............................................................................. 17

Chapter II ....................................................................................................................... 20

Results and Discussion ................................................................................................. 20

II.1. Synthesis of the diene-amine 36 ......................................................................... 21

II.2. Synthesis of different ring size ketoacids ......................................................... 24

II.3. Synthesis of Diels-Alder reaction precursors ..................................................... 45

II.4. Diels-Alder reactions .......................................................................................... 48
II.5. Characterization of cycloadducts ................................................................. 51
Conclusions and Future Studies ............................................................................. 64
Chapter IV .............................................................................................................. 67
Experimental Methods ........................................................................................... 67
References ................................................................................................................ 104
APPENDIX A: 1D-\textsuperscript{1}H NMR Spectra ...................................................... 107
APPENDIX B: 1D-\textsuperscript{13}C NMR Spectra .......................................................... 143
APPENDIX C: 2D- COSY NMR Spectra ................................................................. 179
APPENDIX D: 2D- HMBC NMR Spectra ................................................................. 188
APPENDIX E: 2D- HSQC NMR Spectra ................................................................. 197
APPENDIX F: 2D- NOESY NMR Spectra ............................................................... 206
APPENDIX G: IR Spectra ......................................................................................... 215

Curriculum Vitae
List of Tables, Scheme and Figures

Table 1: Allylic oxidation of 64 and 73 using various conditions of CrO₃............... 36
Table 2: Allylic oxidation of 73, 64 and 65 using various reaction conditions. .......... 38
Table 3: Allylic oxidation of 64, 65, 66 and 73 using Pd(OH)₂ as catalyst. ............ 42
Table 4: Diels-Alder reaction of 41, 42, 43 and 44 using various reaction conditions..... 50
Table 5: The endo/exo ratios obtained from the intramolecular Diels-Alder reaction. .... 61

Scheme 1: Synthetic plans A, B and C used to construct the requisite keto-acids 37-40.25

Figure 1: Structure of morphine................................................................. 2
Figure 2: Structures of various manzamine alkaloids...................................... 3
Figure 3: Synthetic target of the MaGee group............................................ 5
Figure 4: Unsuccessful attempts of intramolecular Michael reaction................... 5
Figure 5: Synthesis of the tricyclic ABC-ring using an intramolecular Diels-Alder strategy.................................................................................................................. 6
Figure 6: Ionic (A), radical (B) and pericyclic (C) reactions............................... 7
Figure 7: Mechanism of the Diels-Alder reaction............................................ 9
Figure 8: Molecular Orbital theory (MO) explains general Diels-Alder reaction. .... 9
Figure 9: Normal electron-demand Diels-Alder reaction.................................. 10
Figure 10: Molecular orbital for general and normal electron-demand Diels-Alder reactions.................................................................................................................. 11
Figure 11: Inverse electron-demand Diels-Alder reaction................................. 12
Figure 12: Molecular orbital for general and inverse-electron-demand Diels-Alder reaction.................................................................................................................. 12
Figure 13: Ortho and para rule ................................................................. 13
Figure 14: Ortho and para rule ................................................................. 14
Figure 15: Endo vs exo transition states and the stereochemical outcome in the
cycloadduct. ........................................................................................... 15
Figure 16: Cisoid vs transoid conformation ............................................ 16
Figure 17: Endo preference in the Diels-Alder ....................................... 17
Figure 18: Martin's study on the intramolecular Diels-Alder reaction of diene-amides... 18
Figure 19: MaGee group's study on the intramolecular Diels-Alder reaction of a diene-
amide containing a six membered ring. .................................................. 18
Figure 20: The proposed retrosynthetic route for this study .................... 21
Figure 21: Preparation of deconjugated acid 54 ..................................... 22
Figure 22: Mechanism of sorbic acid deconjugation ............................. 22
Figure 23: Preparation of 55 ................................................................. 23
Figure 24: Preparation of tosylate 56 ..................................................... 23
Figure 25: Preparation of diene-amine 36 ............................................. 24
Figure 26: Preparation of dibromoketones 61, 62 and 63 ....................... 26
Figure 27: Mechanism of the bromination reaction ............................... 27
Figure 28: Preparation of unsaturated esters 64, 65 and 66. ................. 27
Figure 29: The Favorskii rearrangement mechanism for the generation of 64 via an
oxyallyl intermediate ............................................................................. 28
Figure 30: Preparation of bromo-esters 67, 68 and 69 ............................ 29
Figure 31: Mechanism of allylic bromination ........................................ 30
Figure 32: Preparation and possible mechanism of hydrolysis/substitution to generate
hydroxyl-acids 70, 71 and 72 ................................................................... 31
Figure 33: Preparation of keto-acids 39 and 40 ......................................................... 33
Figure 34: Mechanism of Jones oxidation ................................................................. 33
Figure 35: General allylic oxidation reaction ............................................................ 34
Figure 36: Preparation of keto-acids 74 and 75 ....................................................... 35
Figure 37: Mechanism of CrO₃ allylic oxidation ....................................................... 36
Figure 38: Preparation of keto-esters 74, 75 and 76 via TBHP oxidation ..................... 37
Figure 39: Formation of mixed peroxides ................................................................. 39
Figure 40: Mechanisms of Rh₂(cap)₄ allylic oxidation ........................................... 40
Figure 41: Preparation of keto-esters 29 and 30 using Pd(OH)$_2$-on-carbon ............ 41
Figure 42: Mechanism of Pd(OH)$_2$-on-carbon allylic oxidation .............................. 42
Figure 43: Preparation of keto-acid 37, 38 and 39 .................................................... 43
Figure 44: Preparation of ester 78 ............................................................................ 44
Figure 45: Preparation of keto-ester 76 .................................................................... 44
Figure 46: Preparation of keto-acid 39 .................................................................... 45
Figure 47: Preparation of the Diels-Alder precursors 41, 42, 43 and 44 ................. 46
Figure 48: Mechanism of acid chloride formation using catalytic DMF and oxalyl chloride .............................................................................................................. 46
Figure 49: Alternate procedure for the preparation of 41 ........................................ 47
Figure 50: The intramolecular Diels-Alder reaction of 41, 42, 43 and 44 ............... 48
Figure 51: Diels-Alder reaction of 42 using p-cymene as solvent ........................... 49
Figure 52: Diels-Alder reaction of 42 in toluene at 140-150 °C ............................... 50
Figure 53: Numbering system for the endo and exo cycloadducts ........................... 52
Figure 54: $^1$H NMR of endo 51 ............................................................................. 53
Figure 55: HSQC of endo 51 .................................................................................. 54
Figure 56: COSY of endo 51 ............................................................. 55
Figure 57: HMBC of endo 51 ............................................................. 55
Figure 58: Chemical shift assignment of protons and carbons in 45 and 46 ............... 56
Figure 59: Chemical shift assignment of protons and carbons in 47 and 48 ............... 56
Figure 60: Chemical shifts assignment of protons and carbons in 49 and 50 ............ 57
Figure 61: Chemical shifts assignment of the protons and carbons in 49 and 50 ........ 57
Figure 62: NOE's observed for cycloducts 45 and 46 ........................................... 58
Figure 63: NOE's observed for cycloadducts 47 and 48 ........................................... 59
Figure 64: NOE's observed for cycloadducts 49 and 50 ........................................... 59
Figure 65: NOE's observed for cycloadducts 51 and 52 ........................................... 60
Figure 66: Endo versus Exo cycloadducts ............................................................ 60
Figure 67: Examples of Diels-Alder reaction on larger ring sizes ............................. 65
Figure 68: Examples of Diels-Alder reaction on different chain lengths ................... 66
Figure 69: Examples of Diels-Alder reaction including different heteroatoms ........... 66
List of Symbols and Abbreviations

- AcOH - Acetic acid
- Ac_2O - Acetic anhydride
- CH_3CN - Acetonitrile
- α - Alpha
- AIBN - Azobis(isobutyronitrile)
- Br_2 - Bromine
- ^{13}C \text{ NMR} - Carbon-13 nuclear magnetic resonance
- CDCl_3 - Chloroform-d
- CCl_4 - Carbon tetrachloride
- CrO_3 - Chromium trioxide
- H_2CrO_3 - Chromous Acid
- Cis - Cisoid
- COSY - Correlation Spectroscopy
- J - Coupling in hertz
- °C - Degree Celsius
- δ - Delta
- DCM - Dichloromethane
- Et_2O - Diethylether
- DMSO - Dimethylsulfoxide
- Rh_2(cap)_4 - Dirhodium (II) tetracaprolatamate
- d - Doublet
- dd - Doublet of doublets
- ddd – Doublet of doublets of doublets
- dt - Doublet of triplets
- dtd - Doublet of triplets of doublets
- EDG - Electron-donating groups
- EWG - Electron-withdrawing groups
- EtOAc - Ethyl acetate
- FT-IR - Fourier transformed infrared spectra
- eq - Equivalents
- \( \gamma \) - Gamma
- g - Gram
- H\(_2\) - Hertz
- HMQC - Heteronuclear Single Quantum Coherence experiment
- HMBC - Heteronuclear Multiple Bond Correlation experiment
- Hex - Hexanes
- HOMO - Highest Occupied Molecular Orbital
- h - Hour
- HCl - Hydrochloric acid
- LAH - lithium aluminum hydride
- LDA - Lithium diisopropylamide
- LUMO - Lowest Unoccupied Molecular Orbital
- MgSO\(_4\) - Magnesium sulfate
- MHz - Megahertz
- MP - Melting point
- Hg - Mercury
- μm - Micrometer
- mL - Milliliter
- mg - Milligram
- mmol - Millimole
- MO - Molecular Orbital theory
- m - Multiplet
- NBS - N-bromosuccinimide
- DMF - N, N-Dimethylformamide
- NMR - Nuclear Magnetic Resonance
- NOESY - Nuclear Overhauser Effect Spectroscopy
- 1D - One-dimensional space
- Pd(OH)_2-C - Palladium hydroxide on carbon (Pearlman’s Catalyst)
- ppm - Parts per million
- KOAc - Potassium acetate
- KBr - Potassium bromide
- K₂CO₃ - Potassium carbonate
- ^1H NMR - Proton nuclear magnetic resonance
- KOH - Potassium hydroxide
- KMnO₄ - Potassium permanganate
- q - Quartet
- rt - Room temperature
- SiO₂ - Silica gel
- s - Singlet
- NaH - Sodium hydride
- NaOMe - Sodium methoxide
- \( S_{N2} \) - Substitution reaction bimolecular
- \( H_2SO_4 \) - Sulfuric acid
- TBHP - tert-butyl-hydroperoxide
- THF - tetrahydrofuran
- TLC - Thin layer chromatography
- 2D - Two-dimensional
- OTs - Tosylate
- TMS - tetramethylsilane
- t - Triplet
- td - Triplet of doublets
- UV - Ultraviolet
- \( H_2O \) - Water
- WHO - World Health Organization
Chapter I.

Introduction

I.1. Background information on the manzamine alkaloids

Natural products - including those derived from terrestrial plants, animal products, marine organisms, and products of microorganism fermentation along with their derivatives have made a major contribution in health care and prevention of diseases for thousands of years.\(^1,2\) Historically, the ancient peoples of China, India, and North Africa wrote down how they used natural products as treatments for many diseases and illnesses. Some of the products they found most useful, and which are still being used today, included garlic prescribed for circulatory disorders, mandrake for pain relief and turmeric to help blood to clot. This historical experience using natural products has provided a basis for the evolution of drugs for medicinal purposes as we know today.\(^3\)

A turning point was in the 19th Century, when Friedrich Sertturner isolated morphine 1 from Papaver Somniferum in 1806 (Figure 1).\(^4\) Others followed, isolating pharmacologically-active components from the plants. The process of separating natural products for medicinal purposes then continued to be a major part of scientific studies. It is interesting to note, however, that according to the World Health Organization (WHO), natural products in traditional medicines are used by almost 80% of the world’s population to deal with their immediate health issues.\(^4\) Today, approximately 50% of the drugs on the market are based on, or derived from natural sources.\(^2\)
Interest in the use of natural products, referred to as secondary metabolites, particularly to underpin the development of new drugs, has become more widespread. With the advance of tools for chemistry and biology, scientists are more able to identify and specify the biological effects of natural compounds on humans. Scientists are also able to examine synergies between compounds, and explore the possibilities for positive therapies on devastating diseases such as cancer and dementia. An integral part of modern organic chemistry is the extraction of bioactive compounds (such as manzamines) from organisms, the determination of their structural forms, and the synthesis of the natural products from natural sources.

The oceans that cover about 70% of the earth’s surface provide significant biodiversity of exploration for drug sources, including the manzamine family of alkaloids. More than 80 β-carboline-containing manzamine alkaloids and manzamine-related alkaloids have been isolated from more than sixteen species of sponges found in the Red Sea, Indonesia, Italy and South Africa, for example. The structure of the manzamine alkaloids is unique because of their unusual tetra- or pentacyclic ring system. Some representative examples of the manzamine alkaloids are shown in Figure 2.
Figure 2: Structures of various manzamine alkaloids.
Manzamines are of particular interest because of their impact on a variety of bioactivities, including neuro-inflammatory diseases. The antimicrobial activities are active in the fight against many forms of bacteria and fungi, such as tuberculosis. Manzamines also display antiparasitic, cytotoxic, pesticidal, insecticidal and antitumor bioactivities, for example. However, due to the prevalence and severity of the impact of infectious diseases such as malaria, this may be where manzamines have their biggest impact.\textsuperscript{5,6,8}

Because of the unique structure and bioactivity of the manzamine alkaloids, scientists, particularly synthetic chemists, have been captivated.\textsuperscript{6} A number of syntheses have been reported on the manzamine family of alkaloids, including manzamine A which was first reported in 1986.\textsuperscript{6} The simplest structure, manzamine C, first synthesized in 1989 by Nakagawa and his colleagues, has also been significantly researched.\textsuperscript{9} However, there is a gap in research on manzamine B, and, as a result, the MaGee Group has focused its attention in this area.

One of the main goals in their approach is to synthesize the ABC tricyclic intermediate \textbf{11}, as this tricyclic core is perceived to be integral for the synthesis of manzamine B and its analogues, as well as manzamine A and its analogues (Figure 3). In synthesizing the ABC tricyclic core, the focus is not only on addressing the stereochemical issues associated with the tricyclic system, but also the functionality required to allow for elaboration of the intermediate to the natural product. The MaGee group initially synthesized the AB-ring system and then looked to use a Michael addition to add the C-ring.\textsuperscript{7} The synthesis of the AB-ring system was successfully completed; however, the main problem appeared during attempted generation of the C-ring. Although the intramolecular Michael addition was carried out under several
reaction conditions, no reaction was observed (Figure 4).\(^7\)

**Figure 3**: Synthetic target of the MaGee group.

![Figure 3](image)

**Figure 4**: Unsuccessful attempts of intramolecular Michael reaction.

![Figure 4](image)

The lack of success resulting from the intramolecular Michael reaction led the group to approach the process from a different angle, namely synthesizing the macrocyclic C-ring first, and then forming the AB bicyclic ring system through the use of an intramolecular Diels-Alder reaction. In order to properly install the correct ABC-stereochemistry, the Diels-Alder reaction had to proceed via an endo transition state, relative to the amide (Figure 5).\(^10\)
I.2. General remarks about pericyclic reactions

Pericyclic reactions are one of three categories of organic reactions: ionic, radical and pericyclic. An ionic reaction occurs by heterolytic bond cleavage in which both electrons of the bond remain with one of the atoms when the bond is broken. On the other hand, homolytic bond cleavage forms radicals; that is each of the atoms reserve one electron resulting from the bond breaking process. Pericyclic reactions break and form new bonds through a single-step process that is without an intermediate being created (Figure 6). This important group of reactions is referred to as “concerted pericyclic reactions,” and includes electrocyclic reactions, sigmatropic rearrangements, group transfer reactions and cycloadditions. Although all of these have a common characteristic of a cyclic transition state, each has individual characteristics not shared by the others. Perhaps the most used pericyclic reaction for the synthesis of natural products is the Diels-Alder reaction, discovered by Diels and Alder in the 1920s. The discovery led to a plethora of papers (more than 17,000) addressing various aspects of
the reaction, including synthetic, mechanistic and theoretical.\textsuperscript{12} The reason for this can perhaps be attributed to the fact that it is suitable for the formation of six-member rings in a highly predictable manner and with a wide substrate scope.\textsuperscript{11,13}

A) Ionic Reaction

![Ionic Reaction](image)

breaking bond results from pairs of electrons moving in a single direction

the nucleophile donates both electrons to form a new bond

B) Radical Reaction

![Radical Reaction](image)

breaking bond results from electrons moving into two other atoms

both components equally donate electrons to form a new bond

C) Pericyclic Reaction

![Pericyclic Reaction](image)

All bond-breaking and bond-making takes place in a single step

Figure 6: Ionic (A), radical (B) and pericyclic (C) reactions.

1.2.1. Pericyclic Diels-Alder reactions

The classical Diels-Alder reaction forms a six-membered ring between a 1, 3-diene and an alkene, commonly referred to as a dienophile, and the reaction is thermally allowed according to Woodward-Hoffmann rules. In the process of this reaction, three $\pi$ bonds are broken, forming two new carbon-carbon (C—C) $\sigma$ bonds and one new (C—C) $\pi$ bond.\textsuperscript{11,12} This Diels-Alder reaction is a [4 $\pi+$2 $\pi$]-cycloaddition reaction based on
4 π electrons from the diene and 2 π electrons of the dienophile, which are an integral part of the bonding change.\textsuperscript{12} A hetero-Diels-Alder reaction occurs when one or more heteroatoms are present as part of the π system in the diene and/or dienophile framework. The Diels-Alder reaction can be carried out under variety of experimental conditions, and can also be intermolecular or intramolecular.\textsuperscript{12,14}

1.2.2. Possible mechanisms and molecular orbital theory of Diels-Alder reactions

There has been much discussion in the literature about the Diels-Alder mechanism; one is a concerted one-step process that includes a synchronous and/or asynchronous transition state, while the other mechanism involves a stepwise two-step process that includes intermediate biradicals or zwitterion (Figure 7).\textsuperscript{14–16} It is commonly accepted, however, that most Diels-Alder reactions are a concerted one-step process because of the retention of stereochemistry. More specifically, any Diels-Alder reaction that involves the use of a symmetrical diene and dienophile most likely follows a synchronous concerted pathway, while the reaction of an unsymmetrical diene and dienophile likely follows an asynchronous mechanism.\textsuperscript{16}

Molecular Orbital theory (MO) helps to explain how this reaction occurs (Figure 8). There is a perfectly symmetrical match between the Highest Occupied Molecular Orbital (HOMO) of the diene and the Lowest Unoccupied Molecular Orbital (LUMO) of the alkene, as there is between the HOMO of the alkene and the LUMO of the diene. These perfectly symmetrical matches allow two pairs of electrons to flow, forming two new bonds between the two molecules.\textsuperscript{14}
Figure 7: Mechanism of the Diels-Alder reaction.

Figure 8: Molecular Orbital theory (MO) explains general Diels-Alder reaction.
I.2.3. Reactivity of Diels-Alder reaction

The suprafacial addition of the in phase interaction of the HOMO of one component and the LUMO of the other that are the closest in energy control the reactivity, regioselectivity and stereochemistry of the Diels-Alder reaction.\textsuperscript{12} The HOMO-LUMO energy separation of components affects the reactivity of the Diels-Alder reaction: the lower the difference in energy, the lower the energy required to get cycloaddition to occur. Electron-donating groups increase the energy of both HOMO and LUMO, while electron-withdrawing substituents lower the energy.\textsuperscript{12} Generally, it can be viewed that the diene acts like a nucleophile, and the dienophile acts like an electrophile. Attaching electron-withdrawing groups (EWG) to the dienophile makes it more reactive because it lowers the energy of dienophile LUMO. In addition, the diene becomes more nucleophilic and reactive when electron-donating groups (EDG) are added because this typically increases the energy of the diene HOMO. This process is called the normal electron-demand Diels-Alder reaction, which leads to types A and B (Figure 9), and its strongest interaction is between the diene HOMO and the dienophile LUMO (Figure 10).\textsuperscript{12,13,17}

![Figure 9: Normal electron-demand Diels-Alder reaction.](image-url)
Figure 10: Molecular orbital for general and normal electron-demand Diels-Alder reactions.

Work has also been conducted on reversing the process, that is where electron-donor substituents are added to the dienophile and the electron-accepting substituents are included in the diene to result in combinations C and D (Figure 11). This is referred to as an inverse-electron-demand Diels-Alder reaction. Based on the substituent effects, in these inverse cases the pairing of diene LUMO and dienophile HOMO will be expected to have the strongest interaction (Figure 12). A third approach to this process, in which both the diene and the dienophile have the same type of substituent, is not common because it leads to poor reactivity.\textsuperscript{12,13,17}
I.2.4. Regioselectivity of Diels-Alder reactions

The overlap of the orbitals that have the largest coefficients determines the regioselectivity of the Diels-Alder reaction. The regioselectivity of the cycloaddition increases as the difference between the orbital coefficients of the two end atoms of the diene and two atoms of dienophile, which form the two σ-bonds, becomes greater.\(^\text{12}\) In order to identify the outcome of combining asymmetrical dienes and dienophiles in a
Diels-Alder reaction, an “ionic” stepwise mechanism is used to illustrate the end of the diene that reacts with the relevant end of the dienophile.

In a normal-demand Diels-Alder reaction, if diene 17 bears an EDG at carbon 1 then, because of resonance, a partial negative charge develops on carbon 4. The greatest diene HOMO coefficient shows up at carbon 4. When the dienophile 18 is substituted with an EWG at carbon 1, a partial positive charge will show up on carbon 2, resulting in the dienophile’s greatest LUMO coefficient appearing at carbon 2. A 1-2, or “ortho”, arrangement of substituents (type A) results from the pairing of these two coefficients, through an aromatic like transition state (Figure 13). The diene in a normal-demand

![Diels-Alder Reaction Diagram](image-url)

Figure 13: Ortho and para rule.
Diels-Alder reaction can also be substituted at carbon 2. In this case a partial negative charge will show up on the neighboring carbon 1, producing the largest HOMO coefficient at carbon 1; pairing this with the dienophile 18 results in a para product (Type B) (Figure 13). These pairings rarely result in meta products because the charges are not in alignment (Figure 14). Similar analyses for the corresponding inverse-demand Diels-Alder reactions leads to similar products seen in types C and D (Figure 11). 11

![Diels-Alder Reaction Diagram]

**Figure 14: Ortho and para rule.**

**I.2.5. Stereochemistry of the Diels-Alder reaction**

The effect of adding substituents on the diene and dienophile has an impact on the stereochemistry of the Diels-Alder reaction as well as on the reactivity and regioselectivity of this reaction. There are two possible transition states, caused by the use of unsymmetrical dienophiles, called the *endo* and *exo* transition states; each leads to a different stereoisomer. In the *endo* transition state, the substituents on the dienophile orient under and/or above the conjugated system of the diene, pointing inwards, while in the *exo* transition state the substituents of the dienophile point away from the conjugated system of the diene. 11,12,18

As the Diels-Alder reaction is a suprafacial concerted reaction, the stereochemical relationships between substituents within the diene, and substituents
within the dienophile, retain the same stereochemistry. However, the stereochemical relationships between the substituents in both diene and dienophile in the product are a direct result of the reaction, depending on their position at the time of collision. Keeping the diene fixed in space, with the dienophile above the diene, the dienophile can be flipped side-to-side, creating an endo and an exo transition state (endo 20 and exo 21). Placing the dienophile below the diene, and flipping it side-to-side creates another two transition states (endo 22 and endo 23), thus producing a total of four stereochemical possibilities. The two exo products are enantiomers, as are the two endo products, while the endo products are diastereoisomers to the exo products (Figure 15).

![Diagram of endo and exo transition states](image)

Figure 15: Endo vs exo transition states and the stereochemical outcome in the cycloadduct.
One noteworthy feature of the Diels-Alder reaction is that reaction only occurs when the diene is in a cisoid conformation. Although the cisoid conformation is the preferred state for Diels-Alder reaction, the relative stability of the two conformations is affected by steric factors, which have an impact on any additions to the diene. For example, substituting position 4 in the cis diene, R in 26 and 27, results in a nonbonded interaction between R and the hydrogen in position 1, which makes it difficult to achieve the cisoid conformation (Figure 16).\textsuperscript{20}

![Cisoid vs transoid conformation.](image)

Figure 16: Cisoid vs transoid conformation.

In most Diels-Alder reactions, products arising from the endo transition state are usually produced in higher amounts than those via the exo transition state. It is argued that the reason for this prevalence is that there are two interactions in the endo transition state, secondary (non-bonding) orbital interactions, along with primary interactions, which lower its energy and produces a faster reaction.\textsuperscript{12,18,19} Although the exo product can be produced as a result of its primary bonding orbital interactions, it is slower, so the fast reaction of the endo transition makes it the major product (Figure 17).\textsuperscript{12,18,19}
1.3. Primary objective of the study

An intramolecular Diels-Alder reaction was applied in the previous work done by the MaGee group to synthesize the ABC-tricyclic core required for their approach to the synthesis of manzamine B and A (Figure 5). When the 10-member macrocyclic enone 14 was subjected to intramolecular Diels-Alder reaction the result was an impressive 25:1 ratio of endo 15 to exo 16 selectivity. This was a completely different result from two related cyclizations: one by Martin and his colleagues, who explored new methods for alkaloid synthesis through an intramolecular Diels-Alder reaction using a similar strategy (30) but without the macrocyclic ring, which resulted in approximately an 8:1 endo 31 to exo 32 (Figure 18). The other cyclization containing a six-member ring, 33, conducted by the MaGee group resulted in approximately a 2:1 endo 34 to exo 35 selectivity ratio (Figure 19). The selectivity ratios that were
produced from these two cyclization approaches were much less than the 25:1 selectivity ratio resulting from using enone 14.

![Figure 18](image1.png)

Figure 18: Martin's study on the intramolecular Diels-Alder reaction of diene-amides.

![Figure 19](image2.png)

Figure 19: MaGee group's study on the intramolecular Diels-Alder reaction of a diene-amide containing a six membered ring.

Based on these very diverse results in selectivity, my research focused on investigating the influence of the ring size in which the dienophile is contained, on endo/exo ratios in the intramolecular Diels-Alder reaction. The questions that formed the focus of this research included the effect of the ring size on the endo/exo ratios, whether this effect is a gradual increase with increases in the ring size (5, 7, 9, and 11) or variable, or whether the ring size has no effect on endo/exo ratios. In addition, this research aimed to determine the reasons behind any effects of the size of the ring on the
endo/exo ratios. In order to examine the impact of each ring size on the endo/exo ratio, the research has involved synthesizing the required medium to macrocyclic C-rings, examining each of 5, 7, 9 and 11 member carbon C-rings.

The main points of the Diels-Alder reaction have been highlighted in this introduction, as they relate to the work of this study; namely investigating the influence of the dienophile ring size on the stereochemical outcome of the intramolecular Diels-Alder reaction. This work correlates with the work of the MaGee Group, which is attempting to synthesize the ABC tricyclic core of manzamine B and its analogues. The following sections address the results of the experiments and discussion of these results. Chapter Two includes the results and discussion. Chapter Three addresses the conclusion and future studies. Chapter Four covers the experimental methodology.
Chapter II

Results and Discussion

The main focus of this project was on investigating the influence of the size of the macrocyclic C-ring on endo/exo ratios in the intramolecular Diels-Alder reaction. Previous work done in the MaGee group showed that when the dienophile was embedded in a 10-member macrocyclic ring the intramolecular Diels-Alder resulted in an impressive 25:1 ratio of endo to exo selectivity; however, when entrenched in a six-membered ring only a 2:1 endo to exo selectivity was obtained (Figures 5 and 22). In order to examine the impact of the C-ring size on the endo/exo ratio, this study first involved synthesizing the required medium to macrocyclic C-rings, examining each of five, seven, nine and eleven-member carbon C-rings 37, 38, 39 and 40 respectively. Then each ring size was coupled with the diene-amine 36, followed by application of the intramolecular Diels-Alder reaction. Finally the cycloadducts were analyzed using NMR experiments and the endo/exo selectivity ratios determined. The proposed retrosynthetic route for this study is outlined in Figure 20.
II.1. Synthesis of the diene-amine 36

Based on the proposed retrosynthetic plan illustrated in Figure 20 the starting materials for this study were diene-amine 36 and ketoacids 37, 38, 39 and 40. The first goal was the synthesis of diene-amine 36, obtained in four steps starting with sorbic acid 53. According to the synthesis outlined by Kamdzhilov and Wirz, deconjugation of sorbic acid 53 with lithium diisopropylamine (LDA) in tetrahydrofuran (THF) produced carboxylic acid 54 (Figure 21). Mechanistically (Figure 22), the most acidic protons in sorbic acid were deprotonated by LDA, followed by protonation at the α–position in the trienolate intermediate to provide deconjugated carboxylic acid 54. The rationale provided for protonation at the α-carbon was that it has a higher negative charge than at the γ– or ε–positions.
Reduction of deconjugated acid 54 using lithium aluminum hydride (LAH) in anhydrous diethylether produced primary alcohol 55 in 52% crude yield (Figure 23). The overall percent yield for this reaction was low compared with what was reported in the literature,\textsuperscript{22} which was 92% yield. However, this was not a big issue because the main goal at this point was to prepare enough diene-amine to couple with the various ketoacids. Analysis of the \textsuperscript{1}H NMR of the crude sample showed that alcohol 55 was the major compound so it was used directly in the next step without any purification since it was discovered that all the impurities and side products could be removed easily in the following step.
The next two steps in the formation of the diene-amine followed the synthesis outlined by Martin and co-workers. First, alcohol 55 was converted to its tosylate 56, using standard conditions, p-toluenesulfonyl chloride and pyridine in CH₂Cl₂ (Figure 24). After purification using SiO₂ chromatography, tosylate 56 was produced in a 25% yield over three steps. It was discovered that the highest yield was obtained when the tosylation reaction was allowed to proceed for just three hours. Longer reaction times resulted in significant loss of material, presumably due to production of a pyridinium ion via a substitution reaction and/or hexatriene via an elimination reaction.

The last step in the synthesis of diene-amine was a simple S_N2 substitution reaction of tosylate 56 with benzyl amine 57. After the work-up, removal of the solvent and purification using Kugelrhör distillation (90 °C, 1 mm of Hg), the diene-amine 36 was obtained in an 81% yield (Figure 26).
The SN2 substitution reaction is not a common way to prepare secondary amines because the N atom in the secondary amine is still nucleophilic and can react with more electrophilic atoms, converting a secondary amine to tertiary amine then to quarternary ammonium salt. However, the SN2 type worked well to generate secondary amine 36 when the tosylate 56 (electrophile) was presented in a limited amount relative to benzyl amine 57 (nucleophile).

II.2. Synthesis of different ring size ketoacids

The synthetic plan required diene-amine 36 and different C-ring sizes of ketoacids as starting materials. With 36 in hand, attention was focused on preparing the various keto-acids required for this study. Five and eleven membered keto-acids 37 and 40 were known in the literature,24–31 but the seven and nine membered keto-acid 38 and 39 were unknown and therefore needed to be prepared for the first time in this study.

1-Cyclopentene-1-carboxylic acid methyl ester, cyclooctanone, cyclodecanone and cyclododecanone, which were commercially available, were used as starting materials to form the five, seven, nine and eleven membered rings respectively. Synthetic plan A, which involved five steps, was followed to prepare the eleven-
membered ring keto-acid 40 in excellent overall yield, and the nine-membered ring
eketo-acid 39 in poor overall yield. Five and seven-membered ring keto-acids 37 and 38, respectively, were prepared over four steps following synthetic plan B. A good yield of the nine-membered ring keto-acid 39 was obtained following synthetic plan C following a seven steps process. All synthetic plans, A, B and C, began with bromination of the respective ketones followed by Favorskii rearrangement to generate α, β-unsaturated carboxylic acid methyl esters (Scheme 1).

Scheme 1: Synthetic plans A, B and C used to construct the requisite keto-acids 37 - 40.
Following the protocols developed by Hoffmann and Vinter\textsuperscript{24} and Wohllebe and Garbisch,\textsuperscript{25} bromination of cyclooctanone 58, cyclodecanone 59 and cyclododecanone 60 provided dibromoketones 61, 62, and 63 in 95\%, 90\% and 96\% yield respectively (Figure 26). The \textsuperscript{1}H-NMR spectra of the dibromoketones illustrated the presence of cis and/or trans isomers depending on the ketone ring size. According to literature, the eight membered ring 58 produced the trans isomer of dibromoketone 61, the ten membered system 59, which is a medium sized ring, produced both isomers cis 62a and trans 62b; however, the trans isomer 62b was reported as the most stable isomer.\textsuperscript{24} The 12-membered ring 60 produced cis isomer 63 because the large ring sizes are relatively free to rotate and more flexible than the small and medium ring sizes.\textsuperscript{24} Even though the reaction is stereospecific, the stereochemistry was not identified, largely because all dibromides underwent the Favorskii rearrangement without any difficulties. It should be noted, however, that in some cases (eg. 63) the trans isomer could be converted to the cis-dibromide if required.\textsuperscript{25}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Preparation of dibromoketones 61, 62 and 63.}
\end{figure}

The mechanism of this reaction presumably starts with a keto-enol tautomerization followed by electrophilic addition to the double bond. Then the bromide ion is used to
deprotonate the oxonium ion (Figure 27). The second equivalent of bromine adds to the
carbon on the other side of the carbonyl group, undoubtedly following the same
pathway, resulting in dibromoketone.

![Mechanism of the bromination reaction.](image)

With the preparation of dibromoketone intermediates 61, 62, and 63 completed,
the Favorskii rearrangement was used to form the corresponding unsaturated esters 64,
65, and 66 in 78% 96% and 89% yield, respectively (Figure 28). It is worthy of note
that this reaction was only reported for the preparation of enoate 66; however, by
applying the same method, enoates 64 and 65 were prepared equally successfully.

![Preparation of unsaturated esters 64, 65 and 66.](image)

The base-catalyzed Favorskii rearrangement is a common way to form α, β-
unsaturated carboxylic acid methyl esters via the reaction of α, α’-dichlorinated or α,
α’-dibrominated ketones with sodium methoxide. When the reaction is conducted on
cyclic substrates the product that results is one carbon smaller in size. It is believed that
the reaction proceeds by initial deprotonation of the α-carbon to form an enolate ion like
61a, which converts to an oxyallyl intermediate 61b after the loss of bromide ion.6 After
the oxallyl cation 61b converts to a cyclopropanone 61c, nucleophilic addition of
methoxide to the carbonyl group results in the cleavage of the C1-C3 bond and loss of
bromide to produce the enoate 64 (Figure 29).32

Figure 29: The Favorskii rearrangement mechanism for the generation of 64 via an
oxyallyl intermediate.

Continuing with the synthetic pathway, the α, β-unsaturated esters 64, 65 and 66
were brominated with N-bromosuccinimide (NBS) to generate bromo-esters 67, 68 and
69 (Figure 30).26 Although the 1H-NMR spectrum of bromo-ester 69 was somewhat
complex, it was comparable to that described in the literature.26 While bromides 67 and
were unknown, the $^1$H-NMR spectra of their crude products were similar to that observed in the $^1$H-NMR spectrum of crude 69, thus providing supportive evidence that preparation of 67 and 68 were successfully completed. Attempts to purify the products resulted in compounds that exhibited similar $^1$H-NMR spectra to the crude mixtures, therefore crude products were used in subsequent reactions.

![Diagram](image.png)

**Figure 30: Preparation of bromo-esters 67, 68 and 69.**

The allylic bromination reaction with NBS follows a radical mechanism; it is important to note that the actual brominating agent is not NBS, but bromine that is generated in situ. AIBN is used as a radical initiator by thermal dissociation of AIBN in which two 2-cyanoprop-2-yl radicals and nitrogen gas are formed (Figure 31). Although two allylic brominations are possible, based on the literature report that outlined the preparation of 69, one major product arises, presumably due to the fact that one of the allyl radicals is more stable due to resonance with the ester carbonyl group. Moreover, the H – C bond dissociation of the hydrogen that is conjugated with the carbonyl is less than the one that is not.
The next step was hydrolysis/substitution of the bromo-esters 67, 68 and 69 under basic conditions to provide the corresponding hydroxy acids 70, 71 and 72. The bromo-esters were dissolved in a minimum amount of dimethyl sulfoxide (DMSO) and then a solution of potassium hydroxide in water was added (Figure 32). The potassium hydroxide solution was added slowly to the reaction mixture due to a very rapid equilibrium that occurs when the methoxide ion serves as a base and deprotonates the carboxylic acid; in other words, the hydrolysis of an ester under basic conditions is an irreversible process (Figure 32). The most likely mechanism of this reaction may be a simple ester hydrolysis followed by $S_N2$ hydroxide substitution of the halide to produce the hydroxy-acids.
Figure 32: Preparation and possible mechanism of hydrolysis/substitution to generate hydroxy-acids 70, 71 and 72.

After stirring the reaction mixtures at room temperature between 1 – 48 h, hydroxy acids 71 and 72 were able to be isolated as their insoluble K salts. After protonation, each could be recrystallized using cold DCM. Hydroxy acid 72 was obtained in an acceptable 35% yield from the starting enoate 69. Unfortunately, hydroxy acid 71 was obtained in a very poor 5% yield. After much experimentation, including modifications in the length of the reaction, there was no improvement in the percentage yield of 71. This poor result perhaps was not surprising as hydroxylation of
secondary alkyl halides using a strong base like hydroxide usually is not very successful as significant elimination often competes to generate alkenes as a major product. Consequently, this led to a different pathway being devised (synthetic plan B), one which did not involve the hydrolysis/substitution reaction to synthesize keto-acid 39.

In the case of hydroxy acid 70, this reaction was examined with modification in the length of the reaction between 1 h to 2 days resulting in no formation of the potassium salt. The reaction mixture was then acidified and extracted with ethyl ether, after removal of the solvent the $^1$H-NMR spectrum showed the absence of hydroxy acid 70. The lack of success in the preparation of hydroxy acid 70 could be due to the uncertainty of the formation of bromo-ester 67 in the previous step. Consequently, a different and shorter synthetic plan (synthetic plan C) not involving either a bromo-ester intermediate or hydroxy acid intermediate was pursued to synthesize keto-acid 38.

The final step in the synthetic pathway A was oxidation of the secondary alcohol to a ketone by using Jones reagent. To this end, hydroxy acids 71 and 72 were dissolved in acetone and treated with Jones reagent (8 N) until the mixture maintained a brown colour. After work-up and removal of the solvent, keto-acid 39 was obtained in 45% yield that was of sufficient purity to be used directly in the next step. When working with keto-acid 72 it was discovered that recrystallization from cold hexane could be used to purify 40, thus resulting in a 60% yield (Figure 33).
Jones reagent, a mixture of potassium dichromate, sulfuric acid and water, is an oxidation agent that is used to oxidize primary alcohols to carboxylic acids, and oxidize secondary alcohols to ketones\textsuperscript{36,37}. Jones reagent with alcohol forms a chromate ester intermediate that generates the corresponding carbonyl compound after elimination of chromium (IV) in the form of $\text{H}_2\text{CrO}_3$ (Figure 34).\textsuperscript{38}

With the preparation of the eleven-membered ring keto-acid 40 being complete and the limited success in the preparation of the nine-membered ring keto-acid 39, attention was then concentrated on preparing the five and seven membered ring
analogues, 37 and 38, as well as finding an improved method for production of the nine-membered keto-acid 39. A four-step route, synthetic plan B, which is shown in Scheme 1, was applied to synthesis of the remaining keto-acids; the key step in this process was the allylic oxidation of unsaturated esters to generate keto-esters (Figure 35). The five-membered unsaturated ester 73 was commercially available, while the seven-membered unsaturated ester 64 and the nine-membered ester 65 were prepared following the previous method shown in Figures 29 and 30. Three different oxidation methods were examined: chromium trioxide (CrO₃) in a mixture of acetic anhydride and acetic acid,²⁷ and tert-butyl-hydroperoxide oxidation catalyzed with carbon (Pd(OH)₂-C),³⁰ or dirhodium (II) caprolactamate (Rh₂(cap)₄).²⁸,²⁹

![Figure 35: General allylic oxidation reaction.](image)

Following the procedure reported by Davies and co-workers,²⁷ allylic oxidation of unsaturated ester 73 using 0.45 eq of CrO₃ with a mixture of acetic anhydride and acetic acid in DCM produced keto-ester 74 in only 6% yield (Table 1, Entry 1). The resulting yield was very poor compared to the 60% yield that was reported in the literature.²⁷ Upon repeating the reaction conditions but with minor modification in the length of the reaction from 0.5 h to 48 h, no increase in the percentage yield (Table 1, Entry 2) was
observed. This reaction was examined two more times with modification in both time of the reaction and quantity of CrO\(_3\). The best yield, 36\% of keto-ester 74, was obtained when 1.7 eq of CrO\(_3\) was used and the reaction mixture allowed to stir for 48 h (Figure 36 and Table 1, Entry 4). Analogous allylic oxidation on unsaturated ester 64 was carried out under these optimized conditions (1.7 eq of CrO\(_3\)/48 h) and provided keto-ester 75 in only 14\% yield (Figure 36 and Table 1, Entry 5). Finally, following the procedure reported by Lange and Otulakowski to produce methyl 3-oxo-1-cyclohexene-1-carboxylate,\(^{39}\) unsaturated ester 64 was dissolved in benzene and treated with a solution of 3 eq of CrO\(_3\) in acetic anhydride and acetic acid. After work-up and SiO\(_2\) flash chromatography keto-ester 75 was again obtained in poor yield, 6\% (Table 1, Entry 6).

![Figure 36: Preparation of keto-acids 74 and 75.](image)

The proposed mechanistic pathway\(^{30}\) for the CrO\(_3\) allylic oxidation is shown in Figure 37 using intermediate 64 as the model olefinic substrate. Initially, reaction of CrO\(_3\) with acetic acid and acetic anhydride results in chromium trioxide radical, which in turn abstracts a hydrogen atom from the allylic position of 64 to produce an allylic radical 64g. Chromium trioxide radical can then capture the allylic radical 64g to form a chromate ester 64f, which upon elimination of HCrO\(_3\) produces the carbonyl 75.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Product</th>
<th>CrO₃ (eq)</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>74</td>
<td>0.45</td>
<td>DCM</td>
<td>30 min</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>74</td>
<td>0.45</td>
<td>DCM</td>
<td>48 h</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>74</td>
<td>1.7</td>
<td>DCM</td>
<td>4 h</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>74</td>
<td>1.7</td>
<td>DCM</td>
<td>48 h</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>75</td>
<td>1.7</td>
<td>DCM</td>
<td>48 h</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>75</td>
<td>3</td>
<td>benzene</td>
<td>10 min</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 1: Allylic oxidation of 64 and 73 using various conditions of CrO₃.

![Mechanism diagram](image)

Figure 37: Mechanism of CrO₃ allylic oxidation.

Given the lack of success with using CrO₃, another allylic oxidation protocol was examined using tert-butyl hydroperoxide (TBHP) as the oxidant and dirhodium caprolactamate, Rh₂(cap)₄, as catalyst.²⁸,²⁹ Because of the ability of the tert-butylperoxy radical to remove a hydrogen atom from an active site with a low carbon-hydrogen
dissociation energy, TBHP has been extensively investigated as one of the most promising oxidants to effect allylic oxidations, especially conditions that are conducive for catalytic methods. One of the primary reasons for this interest is that TBHP is a cheap, readily available and stable oxidant.

With renewed vigour, enoates 73, 64 and 65 were subjected to reaction with TBHP under various conditions (Table 2) to generate keto-esters 74, 75 and 76 respectively (Figure 38). Table 2 summarizes all the reactions that were attempted and what was observed was that the percentage conversion was generally increased with an increase in the number of molar equivalents of TBHP. The rate of oxidation was increased in relation to an increase in reaction temperature to 40 °C from room temperature, and that it was best to add the Rh2(cap)₄ catalyst in two portions, first to initiate the reaction, and then after 24 h to complete the conversion. The best results delivered keto-esters 74, 75 and 76 in 37%, 30% and 10% respectively.

![Figure 38: Preparation of keto-esters 74, 75 and 76 via TBHP oxidation.](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Product</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>76</td>
<td>Rh₂(cap)₄ (2 mol %), TBHP (10 eq), DCM, reflux</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>76</td>
<td>Rh₂(cap)₄ (2 mol %), TBHP (10 eq), K₂CO₃ (0.5 eq), DCM, reflux</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>76</td>
<td>Rh₂(cap)₄ (1 mol%), TBHP (10 eq), DCM, rt</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>74</td>
<td>Rh₂(cap)₄ (0.1 mol%), TBHP (5 eq), K₂CO₃ (0.5 eq), DCM, rt</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>74</td>
<td>Rh₂(cap)₄ (1 mol%), TBHP (5 eq), K₂CO₃ (0.5 eq), DCM, reflux</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>74</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>75</td>
<td>Rh₂(cap)₄ (1 mol%), TBHP (10 eq), DCM, reflux</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>76</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2: Allylic oxidation of 73, 64 and 65 using various reaction conditions.

These results were consistent with the impact of the ester functionality as an electron-withdrawing substituent and the possibility of forming mixed peroxide side products. According to a study reported by Doyle and co-workers, cycloalkenes with electron-donating substituents are easier to oxidize than those with electron-withdrawing substituents. As shown in Figure 42 and using intermediate 73 as the model olefinic substrate, the generation of mixed peroxides 73c, 73d and 73e as side products is in agreement with the formation of intermediate allyl 73a and 73b radicals, that react with
tert-butylperoxy radical, and leads to the formation of mixed peroxides (Figure 39) with the main enedione 74 (Figure 38). This process also applies to olefins 64 and 65.29

![Figure 39: Formation of mixed peroxides.](image)

Mechanistically (Figure 40), 1-electron oxidation between Rh$_2$(cap)$_4$ and TBHP generates intermediate II. Under the reaction conditions and via oxidative transformation intermediate II can be converted to dirhodium peroxyether complex III. tert-Butoxy radical I is able to abstract the hydrogen atom from the allylic position in the enone to generate radical IV, followed by regeneration of Rh$_2$(cap)$_4$ as Rh$_2^{4+}$ and formation of mixed peroxide V by ligand transfer of the metal-bound peroxide to the carbon-centered radical. Finally, generation of enedione is obtained after fast decomposition of intermediate V.28 Another way to represent this Rh$_2$(cap)$_4$ allylic oxidation is shown in Figure 40, B.29
Given the limited success of the Rh catalyzed allylic oxidation, a third allylic oxidation method was investigated, this involved using a mixture of TBHP, Pd(OH)$_2$-on-carbon and K$_2$CO$_3$ in DCM (Figure 41). Following literature protocol (Table 3,
Entry 1), 5 eq of TBHP, 10 mol % of 20% Pd(OH)$_2$-on-carbon and 0.25 eq of K$_2$CO$_3$ in DCM were combined with enone 64 and resulted in a 24% yield of enedione 75. Increasing the quantity of the catalyst from 10 to 15 mol % of 20% Pd(OH)$_2$-on-carbon produced ene-one ester 75 in a good yield (75%) compared with the first trial (Table 3, Entry 2). Analogous allylic oxidation on unsaturated ester 73 was carried out under these optimized conditions (15 mol % of 20% Pd(OH)$_2$-on-carbon) to provide keto-ester 74 in 21% yield, which was poor compared with the yield that was reported in the literature (81%). Unfortunately, when the reaction was attempted on the nine-membered enoate 65 and eleven-membered enoate 66 a myriad of compounds were produced, none of which that could be ascribed to the desired products (Table 3, Entry 2). The proposed mechanistic pathway for the Pd(OH)$_2$-on-carbon allylic oxidation, is similar to the CrO$_3$ mechanism (Figure 37), and is shown in Figure 42 using intermediate 64 as the model olefinic substrate.$^{30}$

![Figure 41](image_url)

Figure 41: Preparation of keto-esters 29 and 30 using Pd(OH)$_2$-on-carbon.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>Product</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>75</td>
<td>Pd(OH)$_2$-C (10 mol%), TBHP (5 eq), K$_2$CO$_3$ 0.25 eq, DCM, rt</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>74</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>64</td>
<td>75</td>
<td></td>
<td>Pd(OH)$_2$-C (15 mol%), TBHP (5 eq), K$_2$CO$_3$</td>
<td>75</td>
</tr>
<tr>
<td>65</td>
<td>76</td>
<td></td>
<td>0.25 eq, DCM, rt</td>
<td>0</td>
</tr>
<tr>
<td>66</td>
<td>77</td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: Allylic oxidation of 64, 65, 66 and 73 using Pd(OH)$_2$ as catalyst.

Figure 42: Mechanism of Pd(OH)$_2$-on-carbon allylic oxidation.

The final step in the synthetic plan B involved hydrolysis of the ester to a carboxylic acid under basic condition to generate keto-acids. To achieve this, keto-esters 74, 75 and 76 in methanol were treated with a solution of potassium carbonate in water.
followed by acetic work-up (Figure 43). The five-membered ring keto-acid 37, seven-membered ring keto-acid 38 and nine-membered ring 39 were obtained in 62%, 67% and 86% yields, respectively. It is worthwhile to mention that hydrolysis of 74 using Na$_2$CO$_3$ was reported and it produced 37 in only 45% yield.$^{31}$

![Figure 43: Preparation of keto-acid 37, 38 and 39.](image)

With the five, seven and eleven-membered ring keto-acids 37, 38 and 40 being on hand, and with the limited success in the preparation of the nine-membered ring keto-acid 39 following synthetic plan A and synthetic plan B, an alternative synthetic plan C was devised to make sufficient quantities of the nine-membered keto-acid 39. As in previous routes this plan started with bromination of cyclodecanone 60 to generate $\alpha$, $\alpha'$-dibromo-ketone 63 (Figure 26). This was followed by formation of $\alpha$, $\beta$-unsaturated carboxylic acid methyl ester 66 via the base-catalyzed Favorskii rearrangement (Figure 28). Then, application of allylic bromination with NBS under thermal conditions provided bromo-ester 68 (Figure 30). Treatment of bromo-ester 68 with 5 eq. of potassium acetate (KOAc) in dimethyl sulfoxide (DMSO) at 80-100 °C for 72 h provided aceto-ester 78 as a pale yellow oil in 51% yield after purification via SiO$_2$ column chromatography (Figure 44).
With the oxidation now completed in an acceptable yield, ester 78 was readily hydrolyzed at room temperature with an excess of potassium carbonate in methanol to give the allylic alcohol 79 as a colourless oil in 75% yield (Figure 45). Based on the $^1$H and $^{13}$C NMR data of crude 79, it was of sufficient purity for direct use in the next step without any purification. Jones oxidation on hydroxy-ester 79 was carried out under the conditions that were used for hydroxy acids 71 and 72 to generate keto-ester 76 (Figure 45). After work-up and removal of the solvent, 76 was obtained as a colorless oil in 77% yield that was used directly in the next step without any purification.

With a good amount of keto-ester 76 on hand, the final step of the synthetic pathway C was set. Therefore, a mixture of keto-ester 76 in methanol was treated with a
solution of potassium carbonate in water, followed by acetic work-up to give the nine-membered ring keto-acid 39 as a beige solid in 86% yield (Figure 46).

Following various synthetic pathways, five, seven, nine and eleven-membered ring keto-acids were successfully prepared. These keto-acids were now available to be coupled with diene-amine 36 to form the amide Diels-Alder reaction precursors.

**II.3. Synthesis of Diels-Alder reaction precursors**

With the synthesis of the required components now completed, keto-acids 37, 38, 39 and 40 and diene-amine 36, the stage was set for coupling (Figure 23). To accomplish this, keto-acids 37 – 40 were first converted to their acid chlorides via treatment with oxalyl chloride in DCM that contained a catalytic amount (0.1 eq) of dimethylformamide (DMF) (Figure 47). After heating at reflux for 1 h the solvent was removed, and the formation of acid chloride was checked using $^{13}$C NMR by observing the downfield shift of the carbonyl carbon. It should be noted that DMF was used as a catalyst as it reacted with oxalyl chloride to give a chloro-iminium intermediate that reacted with the carboxylic acid to form the acid chloride and regenerate the DMF.
catalyst (Figure 48). This method provided better results than using either oxalyl chloride by itself or thionyl chloride.

Figure 47: Preparation of the Diels-Alder precursors 41, 42, 43 and 44.

Figure 48: Mechanism of acid chloride formation using catalytic DMF and oxalyl chloride.
With formation of the acid chlorides confirmed, each was treated with Hunig’s base (1.5 eq) and diene-amine 36 (1 eq). After stirring overnight at room temperature, work-up and purification via SiO$_2$ flash chromatography provided amides 41, 42, 43 and 44 in 11%, 65%, 87% and 65% yields, respectively.

Due to the poor yield (11%) resulting from the coupling of 37 with 36 via the acid chloride, an alternative pathway was investigated. Thus, N-methylmorpholine was added slowly to a cold solution of keto-acid 37 and isobutychloroformate in DCM$^{40}$ (Figure 49). After stirring for 30 minutes at -5 to -10 °C, cold 36 was added slowly and the reaction mixture was allowed to gradually warm to room temperature and stir overnight. Gratifyingly, this procedure routinely generated amide 41 in an acceptable 57% yield.

Figure 49: Alternate procedure for the preparation of 41.

$^1$H NMR analysis of the amide intermediates proved to be very difficult. This was due to the presence of two amide rotamers in each $^1$H spectrum, thus causing the peaks to be very broad and difficult to interpret. There was no debate that the correct compounds had been synthesized, as the $^1$H spectra of amide intermediates involving five, seven, nine and eleven-membered rings 41, 42, 43 and 44 were very similar to $^1$H
spectra of the amide intermediates involving the six and ten-membered rings 33 and 14, as reported by the MaGee group in their study on the manzamine alkaloids. Moreover, the IR spectra and $^{13}$C NMR spectra clearly indicated the presence of the ketone and amide carbonyls (see experimental for details). Once it was clear that the correct precursors were obtained, attention was focused on the intramolecular Diels-Alder reactions.

**II.4. Diels-Alder reactions**

A thermal Diels-Alder reaction was performed on amide intermediates 41, 42, 43 and 44 (Figure 50). A solution of each Diels-Alder reaction precursor in toluene was degassed by bubbling argon through it for 30 minutes. The solution, under an inert argon atmosphere, was then stirred and heated at reflux.

Figure 50: The intramolecular Diels-Alder reaction of 41, 42, 43 and 44.
Monitoring the reaction to ensure completion proved cumbersome as it required the reaction to be stopped, an aliquot taken from the sample and analysis by $^1$H NMR. If incomplete, then the solution was degassed once again and then heated at reflux for an additional period of time (Table 4). As indicated in the table not all precursors underwent cycloaddition at the same rate. For instance, amide intermediate 41 required 120 h, while amide intermediates 43 and 44 required 192 h. However, in the case of amide intermediate 42 no reaction was observed after 192 h of refluxing in toluene.

In an attempt to get 42 to undergo cycloaddition the reaction was repeated using $p$-cymene as solvent and heating at 177 °C. After refluxing for 96 h the $^1$H NMR was taken, but it was difficult to interpret due to residual $p$-cymene and significant starting material and/or product decomposition. This presumably occurred since the high temperature decomposed the precursor 42 (Figure 51, Table 4, Entry 5).

![Figure 51: Diels-Alder reaction of 42 using p-cymene as solvent.](image)

With the miserable failure of applying Diels-Alder reaction on precursor 42 using toluene and $p$-cymene, it appeared that the boiling point of toluene was too low and the boiling point of $p$-cymene was too high for this reaction to be successful. Therefore, the reaction in toluene was reexamined using a sealed tube, as typically this allows for an
increase in the internal pressure of the reaction vessel, which in turn allows the use of solvent above its normal boiling point. With this in mind, after bubbling argon through the reaction mixture of toluene and precursor 42, the tube was sealed and heated at 140–150 °C for 288 h to give cycloadducts 47 and 48 (Figure 52, Table 4, Entry 6).

![Diels-Alder reaction of 42 in toluene at 140 - 150 °C.](image)

**Figure 52: Diels-Alder reaction of 42 in toluene at 140 - 150 °C.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Solvent</th>
<th>Temperature °C</th>
<th>Time (h)</th>
<th>Endo:Exo ratio</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>toluene</td>
<td>113</td>
<td>120</td>
<td>≈ 2:1</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>toluene</td>
<td>113</td>
<td>192</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>toluene</td>
<td>113</td>
<td>192</td>
<td>≈ 18:1</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>toluene</td>
<td>113</td>
<td>192</td>
<td>≈ 5:4:1</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>p-cymene</td>
<td>177</td>
<td>96</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>toluene</td>
<td>140–150</td>
<td>288</td>
<td>≈ 2:1</td>
<td>33</td>
</tr>
</tbody>
</table>

**Table 4: Diels-Alder reaction of 41, 42, 43 and 44 using various reaction conditions.**
II.5. Characterization of cycloadducts

With all cycloadditions now completed, attention was focused on characterizing each cycloadduct that resulted from the Diels-Alder reaction. Endo 51 and exo 52 were used as model substrates to see what NMR experiments were needed in order to unequivocally determine the stereochemistries. Whatever information was gleaned would be applied to all of the other cycloadducts. As mentioned earlier, as the product arising from an endo transition state usually results more frequently than one via the exo transition state, the major product was tentatively assigned as endo 51 and the minor as exo 52. To support this assignment, the $^1$H NMR of both isomers, endo 51 and exo 52, were compared with the $^1$H NMR data of the endo and exo isomers Jordan Donahue obtained using the ten-membered C-ring, as she had already conclusively determined their stereochemistries. They were found to be very similar.

Further, molecular modeling, IR spectroscopy and NMR experiments including $^{13}$C, $^1$H, COSY, HMQC, HMBC and NOESY were used to characterize each cycloadduct. Although IR spectroscopy did not provide any information about stereochemistry it was used to determine the functional groups present in the compound. The IR spectra of the endo and exo cycloadducts showed the presence of sp$^2$-hybridized CH bonds of the benzene ring and the sp$^3$- hybridized CH bonds. In addition, two strong vibrations in the carbonyl range were observed along with the aromatic ring vibrations.

In order to determine the endo 51 and exo 52 cycloadducts, with respect to the amide functionality, proton 5, which is attached to C1, and proton 10, which is attached to C5, needed to be located. Once this was done, then running an NOESY experiment would allow for confirmation of which isomer was which (Figure 53). Proton 5 and
proton 10 were located by using one-dimensional and two-dimensional NMR experiments.

Figure 53: Numbering system for the endo and exo cycloadducts.

Analysis of the 1D – $^1$H NMR provided some information, however, it was impossible to determine all the chemical shifts and multiplicities of all individual protons due to the overlapping of the chemical shifts in the system. Regardless, the information that could be gleaned included the chemical shifts of protons 13, 14, 15, 16 and 17 in the aromatic system in the range of 7.38-7.06 ppm in 51 and 7.45-7.19 ppm in 52. Also, the chemical shifts of protons 11 and 12 from the benzyl methylene were determined, which were 4.54 ppm and 4.44 ppm in 51 and 4.59 ppm and 4.55 ppm in 52. In addition, protons with chemical shifts of 5.65 ppm and 5.57 in 51 and 5.73 ppm and 5.34 ppm in 52 were assigned as protons 6 and 7. Figure 54 illustrates the $^1$H of endo 51 as an example of a $^1$H analysis.
Analysis of the 1D – $^{13}$C also provided some information including the chemical shifts of the ketone carbon (C6), which has the chemical shift of 214.1 ppm in 51 and 215.2 ppm in 52. The chemical shift of the amide carbon (C16) was 172.4 ppm in 51 and 173.0 ppm in 52. Also, the carbons that appeared in the range between 120 and 140 ppm were assigned as the aromatic and alkene carbons in both 51 and 52. Although 1D – NMR did not provided definitive information, this information was developed using 2D – NMR.

Using 2D – HSQC it was possible to identify some of the proton-carbon connectivities in the cycloadducts, as well as the carbonyl carbons (C6 and C16) and the quaternary carbons (C15 and C20). In the HSQC spectrum, the red peaks corresponded to the methylene groups (CH$_2$), in which all of its carbons were directly connected to two protons, and the blue peaks corresponded to methine (CH) groups. Cycloadducts 51 and 52 had a few CH groups, namely the aromatic carbons, alkene, C1 and C5. It was possible to distinguish the protons correlated to the carbons in the aromatic and alkene
range; the remaining two protons were assigned as protons 5 and 10. Figure 55 illustrates the HSQC of endo 51 as an example of an HSQC analysis.

![Diagram of alkenes and aromatic systems]

Figure 55: HSQC of endo 51.

In the 2D – COSY spectrum, which identifies protons coupled to other protons often via three bonds, one of these two protons showed coupling with proton 6 and proton 4. Therefore, this proton was assigned as proton 5 (Figure 56), and the other proton was assigned as proton 10. To confirm this, using 2D – HMBC in 51, a correlation between proton 10 and a number of carbons, C6 (214.2 ppm), C16 (172.4 ppm), C3 (125.1 ppm), C15 (45.5 ppm), C1 (35.4 ppm) and C4 (25.4 ppm) were observed (Figure 57). This substantiated the assignments of proton 5 and proton 10.
Figure 56: COSY of endo 51.

Figure 57: HMBC of endo 51.
Analysis of the $^1$H, $^{13}$C, HSQC, COSY and HMBC spectra for all cycloadducts, in an analogous manner to what was done in the case of 51 and 52, allowed the assignment of a number of protons and carbons for each cycloadduct, which are summarized in Figures 58-61.

Figure 58: Chemical shift assignment of protons and carbons in 45 and 46.

Figure 59: Chemical shift assignment of protons and carbons in 47 and 48.
Figure 60: Chemical shifts assignment of protons and carbons in 49 and 50.

Figure 61: Chemical shifts assignment of the protons and carbons in 49 and 50.

After identifying most of protons and carbons in the cycloadducts, NOESY spectra were recorded. The NOESY experiment gives information about which protons are close in space even though they are not bonded; therefore, analysis of the NOESY
spectra confirmed the determination of endo and exo cycloadducts (Figure 66). In the case of endo 51 for example, NOE correlations were observed between proton 5 on C1 (3.21 ppm) and a proton on C14 (1.62 ppm) in the macrocycle ring. As well, correlations were observed between proton 5 and both proton 6 on C2 (5.57 ppm) and proton 4 on C18 (2.20 ppm). However, no NOE correlation was reported between proton 5 and proton 10 (Figure 53 and 65). For the exo product 52, unlike endo 51, a strong NOE correlation was observed between proton 5 on C1 (2.47 ppm) and proton 10 on C5 (2.79 ppm) (Figure 53 and 65). In general, the main difference between endo and exo products was that in all exo products the NOE experiments showed strong correlations between proton 5 on C1 and proton 10 on C5; however, these correlations were absent between these particular protons (proton 5 and 10) in all endo products. Figures 62-65 illustrate the NOESY of cycloadducts 45-52.

Figure 62: NOE’s observed for cycloadducts 45 and 46.
Figure 63: NOE’s observed for cycloadducts 47 and 48.

Figure 64: NOE’s observed for cycloadducts 49 and 50.
Figure 65: NOE’s observed for cycloadducts 51 and 52.

Figure 66: Endo versus Exo cycloadducts.

\( n = 1, 3, 5 \) and 7
The endo/exo ratios resulting from each Diels-Alder reaction were determined after SiO₂ flash chromatography. This ratio was the same as that observed in the crude \(^1\)H NMR spectra obtained immediately after evaporation of the solvent. Amides 41 and 42, which involved five and seven-membered C-rings respectively, produced a ratio of 2:1 endo cycloadduct (45 and 47):exo cycloadduct (46 and 48). In the case of amide 43, which had a nine-membered C-ring, the endo selectivity increased to a ratio of 18:1 endo cycloadduct 49:exo cycloadduct 50 being obtained. In contrast, amide 44, with an eleven-membered C-ring, produced only a ratio of 5.4:1 endo cycloadduct 51:exo cycloadduct 52. Moreover, the previous study reported by the MaGee group indicated that amide intermediates involving six and ten-membered C-rings produced 2:1 and 25:1 endo:exo respectively.\(^{10}\) Each Diels-Alder reaction was conducted multiple times to ensure consistency of results. The results of all the experiments showing endo/exo ratios are summarized in Table 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>C-ring size</th>
<th>Endo/Exo ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>18:1</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>25:1</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>5.4:1</td>
</tr>
</tbody>
</table>

Table 5: The endo/exo ratios obtained from the intramolecular Diels-Alder reaction.
The size of the C-ring, which contains the dienophile, had an effect in the endo/exo selectivity ratio (Table 6). In general, a combination of non-bonded interactions, torsional and angle strains in the chain linking the diene and dienophile, the position of the acyl carbon which attaches to the nitrogen atom, are the effective factors that influence the stereochemical outcome in the intramolecular Diels-Alder reaction.\textsuperscript{21,41,42} Taking into account the nature of our Diels-Alder precursors, torsional and angle strains likely affect the sterochemical outcomes equally due to the linking chains between the dienes and dienophiles remaining the same in all the Diels-Alder precursors investigated in this study. Also, the effect of the acyl carbon location attaching to the nitrogen atom should be the same in all of the cyclizations. The only difference in all of the precursors was the size of the C-ring; therefore, it appears that the differences in the selectivity ratio’s could be due to the effect of the non-bonded interactions. Each ring size has different conformational flexibility in which the ring flexibility increases as the C-ring size increases. It is these differences in non-bonded interactions that we believe plays the major role in the sterochemical outcome.

Finally it is worth mentioning that, in general, substituting the dienophile with an electron-withdrawing group increases the rate of the Diels-Alder reaction by lowering of the energy of the dienophile LUMO.\textsuperscript{42} Surprisingly, in the cyclization reactions in this study the electron-withdrawing group (carbonyl group) did not appear to increase the rate of the reactions when compared with Martin’s cyclization (Figure 18).\textsuperscript{21} In Martin’s studies, when the dienophile contained one electron-withdrawing group, an 83% yield of cycloadduct was obtained after heating the reaction mixture for two hours at 80 °C.\textsuperscript{21} In contrast, our cyclization reactions provided lower yields (64-33%) and required longer reactions times (120-288 h) and higher temperatures (113-150 °C) to occur (Table 4).
The decreased effect of the electron-withdrawing group could be due to reduced overlap between the alkene π-electrons and the carbonyl group in the most reactive ring conformation required for these cyclization reactions to occur.42
Chapter III.

Conclusions and Future Studies

In organic synthesis, the Diels-Alder reaction plays an important role. It is able to form new carbon-carbon bonds in a six-membered ring structure, as well as to create diverse functional groups and new stereocentres in the resulting product. This study set out to explore whether the ring size where the dienophile is contained has an affect on endo/exo ratios in the intramolecular Diels-Alder reaction. Different synthetic pathways were used to prepare the required five, seven, nine and eleven-member carbon C-rings that were coupled with dienamine 36 to generate the requisite Diels-Alder amide precursors.

Thermal Diels-Alder reactions were applied to each of the amide intermediates that produced endo and exo products in different ratios. From the results of this study, the size of the cyclic C-ring clearly impacted the endo/exo ratios. For smaller rings, five through seven, a 2:1 endo:exo was obtained. This ratio increased to 18:1 endo:exo in the case of a nine-member C-ring, 25:1 for a ten-membered ring, and 5.4:1 endo:exo for an eleven-member C-ring. Although the exact reasons for the differences are not completely known, it is clear that the conformation flexibility of the rings plays a major role.

Although the influence of six different C-ring sizes (five, six, seven, nine, ten and eleven-members) on the endo/exo ratios have been studied, it would be useful to make the 8-, 12- and perhaps 14-membered rings as well. The endo/exo ratio is approximately the same in the five, six and seven-membered C-rings; the endo
selectivity increased gradually with the increase of the C-ring size and reached the highest level in the ten-membered C ring. The endo selectivity then decreased sharply when an eleven-membered C-ring was examined. The impact of the C-ring size will gain more clarity as more ring sizes are examined (Figure 67).

Figure 67: Examples of Diels-Alder reaction on larger ring sizes.

Another question relates to the influence of the chain length on the endo:exo ratios. It is expected that the chain length, which includes the diene, will likely have a different influence on the ratio of endo:exo than the ring size does (Figure 68). Another variable to consider would be to look at what effect, if any, the heteroatom has on the stereochemical result of the reaction. For instance, what would the outcome be if a keto-esters were used? How about keto-thioesters (Figure 69)?
Figure 68: Examples of Diels-Alder reaction on different chain lengths.

Figure 69: Examples of Diels-Alder reaction including different heteroatoms.

It is well known that Diels-Alder reactions can be performed under the agency of Lewis acid catalysis. This has not been investigated in this work and is something that should be pursued. This could be important as Lewis acid catalyzed reactions often occur at much lower temperatures than their thermal counterparts and with much better stereochemical control. In addition, if this were to prove successful, then ultimately chiral Lewis acids would need to be investigated, as this would allow for asymmetry to be introduced.
Chapter IV

Experimental Methods

IV.1. General

Reagents purchased from a variety of commercial suppliers were used without further purification. When anhydrous solvents were required, they were selected from a Grubbs column solvent purification system. Silica gel 60 250 µm thickness glass plates were used to perform analytical thin layer chromatography (TLC). Silica gel 60, 1000 µm thick, F254 preparatory plates were used to purify some of the products. Visualization on TLC and preparatory plates was accomplished by short wave UV light or by KMnO4 dip followed by development on a hot plate. Purification by flash column chromatography was performed on silica gel 230-400 mesh purchased from Silicycle with the specified eluent.

NMR spectra were recorded on either a Varian Inova 300 MHz, a Varian Unity 400 MHz, or an Agilent 400 MR DD2 NMR spectrometer at 25 °C. Deuterated chloroform, which contained TMS as an internal standard, was used as the solvent unless otherwise stated. All NMR spectra were processed and analyzed using the Mnova NMR program, Version 9.1.0-14011 or Version 10.0.2-15465 (Santiago de Compostela, Spain). Chemical shifts are reported in parts per million (ppm) and referenced to residual NMR solvent or tetramethylsilane. All proton-proton coupling constants are reported in Hertz (Hz). Fourier transformed infrared spectra (FT-IR) were recorded on a NEXUS 470 Infrared Spectrometer. Neat samples were prepared on a 32 mm diameter KBr window by evaporating the solvent (CH2Cl2) that resulted from dissolving the
compounds in CH$_2$Cl$_2$. A digital Gallenkamp melting point apparatus was used to determine the melting points and are uncorrected.

**IV.2. Preparation of diene-amine 36:**

**IV.2.1. Preparation of (E)-hexa-3, 5-dienoic acid (54):**

Lithium diisopropylamine (LDA; 2M, 100 mL, 200 mmol) was dissolved in anhydrous tetrahydrofuran (300 mL) under an inert argon atmosphere, and then cooled to -10 °C using a salt bath. To the cold LDA solution, sorbic acid 53 (10 g, 90 mmol) in anhydrous tetrahydrofuran (50 mL) was added slowly. After stirring for 2 h at rt, the reaction mixture was then quenched with hydrochloric acid (3M, 300 mL) and extracted with Et$_2$O (100 mL × 3). The combined organic phase was washed with water (100 mL), brine (100 mL), dried over MgSO$_4$ and filtered. Once the solvent was removed under reduced pressure, the resulting brown crude oil 54 (13 g) was used without further purification for the next reaction.

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.34 (dt, $J = 16.9$, 10.2 Hz, 1H), 6.17 (dd, $J = 15.3$, 10.4 Hz, 1H), 5.77 (dt, $J = 14.7$, 7.2 Hz, 1H), 5.19 (d, $J = 16.8$ Hz, 1H), 5.09 (d, $J = 10.5$ Hz, 1H), 3.23 – 3.13 (m, 2H).

$^{13}$C NMR (400 MHz, CDCl$_3$): δ 177.9, 135.1, 134.9, 124.5, 117.4, 37.6.
IV.2.2. Preparation of (E)-hexa-3, 5-dien-1-ol (55):

To a stirring mixture of anhydrous Et₂O (150 mL) and lithium aluminum hydride (4.5 g, 113 mmol) a solution of (E)-hexa-3, 5-dienoic acid 54 (10 g, 89 mmol) and Et₂O (75 mL) was added drop-wise over 25 minutes. After stirring and heating at reflux overnight, the reaction mixture was cooled in an ice water bath, and then quenched by the addition of H₂O (5 mL), NaOH (1M, 5 mL) and H₂O (14 mL). The resulting white aluminum salt was removed by filtering through Celite and the solid was washed with EtOAc (25 mL x 5). The solvent was removed under reduced pressure to give 4.5 g (52%) of (E)-hexa-3, 5-dien-1-ol 55 as a yellowish-brown oil that was used directly in the next step without any purification.

**¹H NMR (400 MHz, CDCl₃):**
δ 6.33 (dt, J = 16.9, 10.2 Hz, 1H), 6.17 (dd, J = 15.2, 10.5 Hz, 1H), 5.67 (dt, J = 14.8, 7.2 Hz, 1H), 5.17 (d, J = 16.7 Hz, 1H), 4.99 (d, J = 10.3 Hz, 1H), 3.68 (t, J = 6.5 Hz, 2H), 2.37 (q, J = 6.5 Hz, 2H).

**¹³C NMR (400 MHz, CDCl₃):**
δ 136.8, 133.6, 130.6, 115.8, 61.8, 35.9.

**FT-IR (cm⁻¹, Neat):**
3386, 2934, 2875, 1682, 1439, 1384, 1050, 972.
IV.2.3. Preparation of (E)-hexa-3,5-dienyl p-toluenesulfonate (56):$^{21}$

![Chemical Reaction Diagram]

Under an inert argon atmosphere a solution of primary alcohol 55 (4.5 g, 45.5 mmol) and pyridine (7.5 mL) in dichloromethane (60 mL) was cooled in an ice water bath. To this, p-toluenesulfonyl chloride (10.8 g, 56.9 mmol) was slowly added over a period of ten minutes; after complete addition the reaction mixture was allowed to stir for 3 h at rt. After removing the solvent using reduced pressure, the resulting product was dissolved in cold HCl (1M, 140 mL) and Et₂O (100 mL × 3) was used to extract the aqueous layer. The combined organic phase was washed with HCl (1M, 40 mL), saturated sodium bicarbonate (50 mL), brine (50 mL), dried over magnesium sulfate and filtered. After removing the solvent under reduced pressure the residue was purified by SiO₂ chromatography (8:1 Hex:EtOAc as eluent) 4.53 g (25% over three steps) of (E)-hexa-3, 5-dienyl p-toluenesulfonate 56 as a colourless oil.

$^1$H NMR (400 MHz, CDCl₃):

δ 7.77 (d, $J$ = 8.3 Hz, 2H), 7.33 (d, $J$=8.3 Hz, 2H),
6.21 (dt, $J$ = 1.69, 10.3 Hz, 1H), 6.02 (dd, $J$ = 15.2, 10.4 Hz, 1H), 5.50 (dt, $J$ = 7.1, 15.1 Hz, 1H),
5.09 (d, $J$ = 16.9 Hz, 1H), 5.00 (d, $J$ = 10.3 Hz, 1H), 4.03 (t, $J$ = 6.7 Hz, 2H), 2.43 (s, 3H), 2.41 (q, 
$J$ = 6.7 Hz, 2H).
$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 144.8, 136.4, 134.1, 133.0, 129.8, 127.9, 116.6, 116.5, 69.5, 32.0, 21.6.

FT-IR (cm$^{-1}$, Neat): 3025, 2926, 1598, 1189, 1176, 968, 917, 665, 555.

**IV.2.4. Preparation of N-benzyl-((E)-hexa-3,5-diene)amine (36):**

![Chemical Reaction Diagram]

In a 100 mL round-bottom flask under an inert argon atmosphere was added benzylamine 57 (9.8 mL, 90 mmol) to a solution of (E)-hexa-3, 5-dienyl p-toluenesulfonate 56 (4.5 g, 18 mmol) in acetonitrile (45 mL) and the reaction mixture was left to stir at reflux for 72 h. After removing the solvent under reduced pressure, the resulting product was dissolved in Et$_2$O (50 mL) and washed with NaOH (70 mL × 2). The aqueous layer was extracted with Et$_2$O (15 mL × 3) and the combined organic layer was then dried over MgSO$_4$ and filtered, followed by removal of the solvent under reduced pressure. Kugelrhor distillation (90 °C, 1 mm of Hg) of the resulting oil gave 3.3 g (81%) of diene-amine 36 as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 – 7.17 (m, 5H), 6.26 (dt, $J$ = 14.9, 10.2 Hz, 1H), 6.06 (dd, $J$ = 14.9, 10.4 Hz 1H), 5.63 (dt, $J$ = 14.8, 7.1 Hz, 1H), 5.08 (d, $J$ = 16.9 Hz, 1H), 4.93
(d, \( J = 9.9 \) Hz, 1H), 3.79 (s, 2H), 2.66 (t, \( J = 6.9 \) Hz, 2H), 2.26 (q, \( J = 7.0 \) Hz, 2H).

\(^{13}\text{C} \text{NMR (400 MHz, CDCl}_3\): \( \delta \) 140.4, 137.1, 132.7, 132.5, 128.4, 128.1, 127.0, 115.4, 53.9, 48.6, 33.1.

\text{FT-IR (cm}^{-1}, \text{Neat):} \) 3028, 2919, 2818, 1650, 1602, 1453, 1120, 1005, 900, 735, 698.

\textit{IV.3. Preparation of keto-acids}

\textit{IV.3.1. General procedure used for preparation of }\( \alpha, \alpha' \) -Dibromocycloalkanones (61, 62 and 63):\(^{24,25}\)

\[\begin{align*}
\text{O} & \quad \text{Br}_2 \\
\text{Br} & \quad \text{Br}
\end{align*}\]  \\
\text{anhydrous ether} & \quad \text{and/or}

\text{58} \ n=1 \\
\text{59} \ n=3 \\
\text{60} \ n=5 \\
\text{n=1 95% trans 61} \\
\text{n=3 90% cis 62a and trans 62b} \\
\text{n=5 96% cis 63}

In a RBF, the cycloalkanone was dissolved in anhydrous diethyl ether and cooled to 0-5 °C in an ice-water bath. As the cooled solution was stirred, bromine (1 eq) was added slowly over a period of 35 minutes. The rate of addition was similar to the bromine uptake by the solution. After removing the ice water bath the reaction mixture was allowed to warm to room temperature and a second equivalent of bromine was added drop-wise at the uptake rate at room temperature. After complete addition of the
second equivalent of bromine the reaction mixture was left to stir for one hour at room temperature, then washed with aqueous Na$_2$S$_2$O$_3$ (2%, 100 mL), 10\% Na$_2$CO$_3$ (90 mL) and water (100 mL). The organic phase was dried over magnesium sulfate (MgSO$_4$), filtered and solvent removed under reduced pressure.

**IV.3.1.1. Preparation of trans-2, 8-dibromocyclooctanone (61):**

Starting with cyclooctanone 58 (15 g, 118 mmol), bromine (12 g, 236 mmol) in Et$_2$O (150 mL) produced 32 g (95\%) of 2, 8-dibromocyclooctanone 61 as an orange oil that was of sufficient purity to use directly in the next step without any purification.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.63 (dd, $J = 11.9$, 4.5 Hz, 2H), 2.39-2.16 (m, 4H), 1.80-1.32 (m, 6H).

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 202.5, 48.1, 35.5, 25.3, 22.8.

FT-IR (cm$^{-1}$, Neat): 2929, 2857, 1718, 630.

**IV.3.1.2. Preparation of cis- and trans-2, 10-dibromocyclodecanone (62a and 62b):**

Starting with cyclodecanone 59 (6 g, 38.9 mmol), bromine (3.8 g, 77.8 mmol) in Et$_2$O (80 mL) produced a 10.9 g (90\%) of 2, 10-dibromocyclodecanone 62a and 62b as a yellow oil which was of sufficient purity to be used directly in the next step.

**Major Isomer:**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.99 (dd, $J = 9.9$, 3.9 Hz, 2H), 2.42-2.16(m, 4H), 1.76-1.12 (m, 10H).

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 198.4, 48.7, 33.9, 25.7, 23.5, 23.1.

FT-IR (cm$^{-1}$, Neat): 2935, 2874, 1724, 1471, 1442, 625.
IV.3.1.3. Preparation of cis-2, 12-dibromocyclododecanone (63):

Cyclododecanone 60 (25 g, 137 mmol), bromine (14 g, 274 mmol) and Et₂O (200 mL) were used. Approximately two-thirds of the way through adding the second amount of bromine, the appearance in the solution of a white crystalline solid resulted in inadequate stirring. Addition of the bromine was stopped; the solid was filtered and washed with a minimum amount of cold Et₂O (20 mL x 2). The filtrate was cooled in an bath and the remaining amount of bromine was added drop-wise to the stirred, cooled solution at the rate of uptake. After all the remaining bromine was added, a white crystalline solid appeared in the solution. The white crystalline solid was filtered, and then washed with cold anhydrous Et₂O (20 ml x2). The filtrate was left to evaporate overnight to give an off white solid. The three fractions of crystalline solid were combined to produce 44.7 g (96%) of 2, 12-dibromocyclododecanone 63 which was of sufficient purity to be used directly in the next step.

**MP:** 126.5-172 °C

**¹H NMR (400 MHz, CDCl₃):** δ 4.99 (dd, J = 8.9, 3.2 Hz, 2H), 2.38-2.24 (m, 2H), 2.07 (m, 2H), 1.04-1.56 (m, 16 H).

**¹³C NMR (400 MHz, CDCl₃):** δ 195.9, 48.6, 32.4, 24.5, 24.4, 22.4, 21.7.

**FT-IR (cm⁻¹, Neat):** 2938, 2865, 1725, 731, 626.
**IV.3.2. General procedure used for preparation of unsaturated esters (64), (65) and (66):**

Under an inert argon atmosphere, a solution of anhydrous benzene and sodium hydride (60 % immersion in paraffin; 1 eq.) was cooled in a bath of ice water. Anhydrous methanol (1 eq.) was added drop-wise to the cold stirring mixture over a period of 35 min. The solution was removed from the ice water bath once the methanol was added, and left to stir for one hour at room temperature. The reaction mixture was then cooled in an ice water bath and dibromoketone in benzene was added portion-wise/drop-wise over a period of 30 minutes. The ice water bath was removed, and the reaction mixture was left to stir at room temperature for approximately 15 minutes. The reaction mixture was then washed with water (85 mL), the layers separated and the aqueous phase extracted with Et₂O (50 mL x3). The combined organic layers were washed with hydrochloric acid (HCl) (5%, 90 mL), brine (90 mL) and then dried over magnesium sulfate. The solvent was removed using reduced pressure and the crude purified via SiO₂ chromatography.
**IV.3.2.1. Preparation of methyl (Z)-cyclohept-1-ene carboxylate (64):**

Starting with 1, 8-dibromocyclooctanone 61 (32 g, 112 mmol), NaH (15.7 g, 394 mmol), methanol (16 mL) in benzene (130 mL), 13.6 g (78%) of methyl (Z)-cyclohept-1-ene carboxylate 64 was obtained after SiO$_2$ column chromatography (25:1 Hex:EtOAc as eluent) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): \[ \delta 7.13 \text{ (t, } J = 6.7 \text{ Hz, } 1\text{H}), 3.67 \text{ (s, } 3\text{H}), 2.53-2.45 \text{ (m, } 2\text{H}), 2.30-2.21 \text{ (m, } 2\text{H}), 1.80-1.69 \text{ (m, } 2\text{H}), 1.57-1.41 \text{ (m, } 4\text{H}). \]

$^{13}$C NMR (400 MHz, CDCl$_3$): \[ \delta 168.4, 144.1, 136.1, 51.4, 31.7, 28.5, 27.1, 25.9, 25.4. \]

FT-IR (cm$^{-1}$, Neat): 2928, 2855, 1714, 1436, 1255, 1203.

**IV.3.2.2. Preparation of methyl (Z)-cyclonona-1-ene carboxylate (65):**

Starting with 1, 10-dibromocyclodecanone (10.9 g, 34.9 mmol), NaH (4.8 g, 122 mmol), methanol (4.5 mL) in benzene (80 mL), 6.1 g (96%) of methyl (Z)-cyclonona-1-ene carboxylate 14 was obtained after SiO$_2$ column chromatography (10:1 Hex:EtOAc as eluent) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): \[ \delta 6.89 \text{ (t, } J = 8.9 \text{ Hz, } 1\text{H}), 3.71 \text{ (s, } 3\text{H}), 2.51-2.38 \text{ (m, } 2\text{H}), 2.32-2.19 \text{ (m, } 2\text{H}), 1.63-1.36 \text{ (m, } 8\text{H}). \]

$^{13}$C NMR (400 MHz, CDCl$_3$): \[ \delta 168.5, 142.6, 132.7, 51.6, 26.9, 25.7, 25.4, 25.2, 25.1, 25.0, 24.9. \]

FT-IR (cm$^{-1}$, Neat): 2927, 2856, 1713, 1640, 1285.

**IV.3.2.3. Preparation of methyl (Z)-cyclodeca-1-ene carboxylate (66):**


Starting with 1, 12-dibromocyclodecanone 63 (44.7 g, 131 mmol), NaH (18.4 g, 460 mmol), methanol (18 mL) in benzene (230 mL), 24.4 g (89%) of methyl (Z)-cycloundeca-1-ene carboxylate 66 was obtained after SiO₂ column chromatography (15:1 Hex:EtOAc as eluent) as a colourless oil.

\[ \delta 6.08 \text{ (t, } J = 8.2 \text{ Hz, } 1H), 3.75 \text{ (s, } 3H), 2.51 \text{ (dd, } J = 12.4, 7.6 \text{ Hz, } 2H), 23 \text{ (t, } J = 6.1 \text{ Hz, } 2H), 1.62-1.47 \text{ (m, } 4H), 1.44-1.13 \text{ (m, } 10 \text{ H).} \]

\[ \delta 168.6, 143.2, 131.3, 50.9, 35.2, 29.5, 26.6, 25.9, 25.5, 25.5, 25.4, 25.2, 24.8. \]

FT-IR (cm⁻¹, Neat): 2928, 2858, 1718, 1639, 1233.

**IV.3.3. General procedure used for preparation of bromo-esters (68) and (69):**

A mixture of unsaturated ester, azobis(isobutyronitrile) (AIBN) (cat.) and N-bromosuccinimide (NBS) (1 eq.) in CCl₄ was stirred and slowly heated at reflux for 2 h. The mixture was cooled to room temperature and the succinimide was filtered off. The filtrate was washed with water (50 mL x2) and then dried over magnesium sulfate. The
product resulting from removal of the solvent under reduced pressure was used directly in the next step without any purification.

**IV.3.3.1. Preparation of methyl (Z)-3-bromocyclonona-1-ene carboxylate (68):**

The reaction was performed using methyl (Z)-cyclonona-1-ene carboxylate 65 (6.1 g, 33.46 mmol), NBS (5.9 g, 33.46 mmol) and CCl₄ (50 mL) to produce 7.7 g (88%) of crude methyl (Z)-3-bromocyclonona-1-ene carboxylate 68 as a light brown oil that was used directly in the next step without any purification.

**1H NMR (400 MHz, CDCl₃):**

δ 7.09 (d, J = 10.6 Hz, 1H), 5.49 (td, J = 12.0, 3.8 Hz, 1H), 3.82 (s, 3H), 2.61-2.27 (m, 3H), 2.28-2.00 (m, 3H), 1.86-1.30 (m, 6H).

**13C NMR (400 MHz, CDCl₃):**

δ 167.6, 141.4, 132.8, 52.1, 47.6, 38.7, 28.3, 27.1, 26.3, 25.7, 25.1.

**FT-IR (cm⁻¹, Neat):**

2929, 2857, 1717, 1639, 1284, 777.

**IV.3.3.2. Preparation of methyl (Z)-3-bromocycloundeca-1-ene carboxylate (69):**

The reaction was performed using methyl (Z)-cycloundeca-1-ene carboxylate 66 (25.4 g, 122 mmol), NBS (21.7 g, 122 mmol) and CCl₄ (200 mL) to produce 32.7 g (97%) of crude methyl (Z)-3-bromocycloundeca-1-ene carboxylate 69 as a light brown oil that was used directly in the next step without any purification.

**1H NMR (400 MHz, CDCl₃):**

δ 6.75 (d, J = 11.6 Hz, 1H), 4.99 (ddd, J = 11.5, 9.0, 6.3 Hz, 1H), 3.75 (s, 3H), 2.65-2.58 (m, 1H), 2.30 (ddd, J = 14.3, 12.1, 3.0 1H), 2.20-2.05 (m, 2H), 1.80-1.01 (m, 12).
\(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \(\delta 167.8, 141.1, 134.5, 52.0, 46.4, 39.7, 27.9, 26.9, 25.8, 24.8, 24.5, 22.4, 22.4\).

FT-IR (cm\(^{-1}\), Neat): 2935, 2862, 1719, 1637, 1283, 1237, 768.

**IV.3.4. Preparation of (Z)-3-hydroxycyclonona-1-ene carboxylic acid (71):**

Bromoester 68 (7.7g, 29.48 mmol) was dissolved in DMSO (15 mL) and a solution of potassium hydroxide (3.3g, 58.96 mmol) in water (6 mL) was added to the reaction mixture. The combined solution was stirred for 48 h at room temperature, and then diluted with H\(_2\)SO\(_4\) (20%, 30 mL) and extracted with Et\(_2\)O (30 mL \(\times\) 3). The combined organic layer was washed with H\(_2\)SO\(_4\) (20%, 35 mL \(\times\) 7) and then dried over MgSO\(_4\), filtered, and then the solvent was removed under reduced pressure. The crude product obtained was recrystallized using cold DCM (20 mL) to give 0.29 g (5%) of hydroxy acid 71 as a white crystalline solid.

**MP:** 145-146 °C

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 6.87 \) (d, \( J = 8.3 \) Hz, 1H), 4.80-4.61 (m, 1H), 2.81-2.67 (m, 1H), 1.97-1.18 (m, 11 H).
\( ^{13} \text{C NMR (400 MHz, CDCl}_3 \): \) \( \delta 171.4, 146.9, 131.1, 70.2, 36.0, 30.9, 27.23, 27.1, 25.5, 23.1. \)

FT-IR (cm\(^{-1}\), Nujol): 3371, 1692, 1665, 1637, 1467, 1192.

**IV.3.5. Preparation of (Z)-3-hydroxycycloundec-1-ene carboxylic acid (72):**

Bromoester 69 (32.7 g, 117 mmol) was dissolved in DMSO (42 mL) and a solution of potassium hydroxide (KOH, 13 g, 235 mmol) in water (23 mL) was added to the reaction mixture. The combined solution was stirred for one hour at room temperature, and then cooled to 5 °C using an ice water bath. The solution was filtered to produce the K\(^+\) salt, which was dissolved in water (70 mL) and H\(_2\)SO\(_4\) (20%, 70 mL) was added. The solid was filtered off to give crude hydroxy acid. The solid was recrystallized using cold DCM (45 mL) to give 8.5 g (34%) of hydroxy acid 72 as a white solid.

**MP:** 148-149 °C

\( ^1 \text{H NMR (400 MHz, CDCl}_3 \): \) \( \delta 6.70 \text{ (d, } J = 10 \text{ Hz, } 1\text{H}), 4.66 \text{ (td, } J = 10.0, 4.0 \text{ Hz, } 1\text{H}), 2.58 \text{ (dtd, } J = 14.1, 4.5, 1.5 \text{ Hz, } 1\text{H}), 2.43 \text{ (dt, } J = 14.5, 7.3 \text{ Hz, } 1\text{H}), 1.92-1.80 \text{ (m, } 1\text{H}), 1.73- \)
$1.58$ (m, 3H), 1.57-1.40 (m, 2H), 1.39-105 (m, 8H).

$^{13}\text{C NMR (400 MHz, CDCl}_3\text{):}$ δ 171.4, 144.6, 133.6, 67.5, 36.5, 26.6, 26.4, 25.8, 25.3, 24.3, 23.7, 22.0.

$\text{FT-IR (cm}^{-1}, \text{Nujol):}$ 3378, 1695, 1637, 1459, 1192.

$\textbf{IV.3.6. Procedure for preparation of aceto-ester (78):}$

In a 100 mL round-bottom flask a mixture of bromo-ketone $69$ (4.4 g, 17 mmol) and KOAc (8.3 g, 84 mmol) in DMSO (34 mL) was stirred at 80-100 °C for 72 h. The reaction mixture was cooled and diluted with water (70 mL) and brine (300 mL), and then extracted with EtOAc ($100 \text{ mL } \times 4$). The combined organic phase was dried over MgSO$_4$, and the solvent was removed under reduced pressure. The residue was purified via SiO$_2$ column chromatography (9:1 Hex:EtOAc as eluent) to give 2.3 g (51%) of aceto-ester $78$ as a pale yellow oil.

$^1\text{H NMR (400 MHz, CDCl}_3\text{):}$ δ 6.65 (d, $J = 8.5$, Hz, 1H), 5.64-5.504 (m, 1H), 3.74 (s, 3H), 2.74 (ddd, $J = 13.9$, 6.3, 3.0 Hz, 1H),
2.20 (ddd, J = 13.6, 11.3, 2.9 Hz, 1H), 2.04 (s, 3H), 1.90-1.30 (m, 10H).

$^{13}$C NMR (400 MHz, CDCl$_3$): δ 170.3, 167.7, 140.3, 133.0, 72.5, 51.9, 32.5, 27.3, 27.0, 25.5, 25.3, 22.8, 21.2.

FT-IR (cm$^{-1}$, Neat): 2931, 1859, 1738, 1655, 1437, 1370, 1239, 1024.

**IV.3.7. Procedure for preparation of hydroxy-ester (79):**

Under an inert argon atmosphere, aceto-ester 78 (2.3 g, 8.5 mmol) was dissolved in methanol (130 mL), and potassium carbonate (4.7 g, 34 mmol) was added. The reaction mixture was left to stir at room temperature until TLC (8:1 Hex:EtOAc) showed complete consumption of starting material. After approximately 3 h a cold aqueous saturated solution of ammonium chloride (300 mL) was added. After stirring for a few minutes the reaction mixture was extracted with Et$_2$O (30 mL × 3), and the combined organic phase was washed with brine (50 mL × 1), dried over MgSO$_4$ and filtered. Removing the solvent under reduced pressure produced 1.4 g (75%) of methyl (Z)-3-hydroxycyclonona-1-ene carboxylate 79 as a colourless oil that was used directly in the next step without any purification.
**IV.3.8. General procedure used for preparation of keto-acids (39) and (40), and keto-ester (79):**

H0 OH

\[
\text{HO} \quad \text{OH} \quad \text{HO} \\
\text{71} \quad \text{72} \quad \text{79} \quad \text{39} \quad \text{40} \quad \text{76}
\]

Hydroxy-acid 71/72 or ester 79 was added to acetone and Jones reagent (8N) was added drop-wise at room temperature until the mixture maintained a brown colour. The reaction mixture was stirred for 15 minutes and then a few drops of iPrOH were
added to the mixture to quench excess Jones reagent. The resulting solution had a blue-green chromium salt precipitate. Water was added to dissolve the salts and the solution was extracted with CH$_2$Cl$_2$ (30 mL × 4). The combined organic phase was dried over MgSO$_4$, filtered and the solvent evaporated.

**IV.3.8.1. Preparation of (Z)-3-oxocyclonona-1-ene carboxylic acid (39):**

Hydroxy-acid 71 (0.29 g, 1.3 mmol) produced 0.11 g (45%) of (Z)-3-oxocyclonona-1-ene carboxylic acid 39 as a beige solid, which was of sufficient purity to be used directly in the next step.

**MP:** 96-97°C

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.18 (s, 1H), 2.74-2.66 (m, 4H), 1.95-1.83 (m, 2H), 1.65-1.52 (m, 4H), 1.45-1.35 (m, 2H).

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 207.5, 172.5, 140.7, 137.0, 41.1, 27.9, 27.0, 26.1, 24.7, 23.3.

FT-IR (cm$^{-1}$, Neat): 3497, 2930, 2858, 1709, 1631, 1219.

**IV.3.8.2. Preparation of (Z)-3-oxocycloundec-1-ene carboxylic acid (40):**

Hydroxy-acid 72 (8.5 g, 40 mmol) produced 5 g (60%) of (Z)-3-oxocycloundec-1-ene carboxylic acid 40 as a white crystalline solid following recrystallization using cold hexane (50 mL).

**MP:** 93-94°C
\( ^1 \)H NMR (400 MHz, CDCl\(_3\)):  \( \delta \) 7.30 (s, 1H), 2.76 (t, \( J = 6.2 \) Hz, 2H), 2.56-2.45 (m, 2H), 1.81-1.73 (m, 2H), 1.64-1.53 (m, 2H), 1.50-1.41 (m, 2H), 1.29-1.15 (m, 6H).

\( ^{13} \)C NMR (400 MHz, CDCl\(_3\)):  \( \delta \) 205.9, 171.7, 140.5, 138.8, 43.9, 26.7, 25.6, 25.5, 25.1, 24.0, 23.7, 22.7.

FT-IR (cm\(^{-1}\), Neat): 3451, 2930, 2860, 1683, 1620, 1427.

**IV.3.8.3. Preparation of methyl (Z)-3-oxocyclonona-1-ene carboxylate (76):**

Hydroxy-ester 79 (1.2 g, 5.3 mmol) produced 0.93 g (77%) of methyl (Z)-3-oxocyclonona-1-ene carboxylate 76 as a colourless oil that was used directly in the next step of the process without any purification.

\( ^1 \)H NMR (400 MHz, CDCl\(_3\)):  \( \delta \) 7.03 (s, 1H), 3.77 (s, 3H), 2.78-2.59 (m, 4H), 1.92-1.78 (m, 2H), 1.55 (m, 4H), 1.44-1.30 (m, 2H).

\( ^{13} \)C NMR (400 MHz, CDCl\(_3\)):  \( \delta \) 207.5, 168.1, 139, 138.1, 52.5, 41.2, 28.2, 17.3, 26.2, 23.2.

FT-IR (cm\(^{-1}\), Neat): 2931, 2860, 1720, 1656, 1470, 1437, 1261, 1214, 1144.
IV.3.9. General procedure for preparation of keto-esters (74) and (75) using Pd(OH)$_2$-on-carbon:

In a 100 mL round-bottom flask, pure unsaturated ester, Pd(OH)$_2$-on-carbon (5 mol %) and K$_2$CO$_3$ (0.13 eq) were dissolved in DCM (15 mL). The mixture was cooled in an ice water bath then tert-butyl-hydroperoxide (TBHP) (2.5 eq) was added and the mixture stirred vigorously. A rubber septum was used to seal the flask and the mixture left to stir at room temperature. After 24 h of stirring, Pd(OH)$_2$-C (2.5 mol %), K$_2$CO$_3$ (0.063 eq) and TBHP (1.25 eq) were added. After another 24 h this process was repeated using the same amount of chemicals. After a further 24 h, a fourth amount of Pd(OH)$_2$-C (5 mol %) was added and allowed to stir for another 24 h. Crude keto-ester resulted after filtration of the reaction mixture, and removal of the solvent under reduced pressure.

IV.3.9.1. Preparation of methyl (Z)-3-oxocyclopent-1-ene carboxylate (74):

Unsaturated ester 73 (1 g, 7.9 mmol) produced 0.22 g (21%) of methyl (Z)-3-oxocyclopent-1-ene carboxylate 27 (0.22 g) after SiO$_2$ flash chromatography (3:1 Hex:EtOAc as eluent) as a colourless oil.
IV.3.9.2. Preparation of (Z)-3-oxy-cyclohept-1-ene carboxylate (75):

Unsaturated ester 13 (1.5 g, 9.7 mmol) produced 1.1 g (70%) of methyl (Z)-3-oxy-cyclohept-1-ene carboxylate 64 after SiO₂ flash chromatography (10:1 Hex:EtOAc as eluent) as a colourless oil. NOTE: This was the best yield obtained, however, yields typically ranged anywhere from 45-70%.

IV.3.10. General procedure used for preparation of keto-esters (74) and (75) using chromium trioxide:

In a round-bottom flask and under an inert argon atmosphere, glacial acetic acid was added slowly to a stirring solution of CrO₃ (1.7 eq) in acetic acid. This mixture was cooled to 0-5 °C in an ice water bath, and left to stir for 2 h. The chromium trioxide solution was then added drop-wise over two hours to a cooled (0-5 °C) solution of unsaturated ester in DCM. Initial addition of the oxidizing reagent turned the color of the mixture to black. The reaction mixture was allowed to stir at room temperature for 48 h. Then KOH was added to neutralize the reaction mixture, the organic layer was separated and the aqueous layer was extracted with DCM (40 mL × 4). The combined
organic layer was washed with aqueous saturated solution of NaHCO$_3$ (150 mL × 2) and brine (150 mL), dried over MgSO$_4$ and then filtered. Crude keto-ester resulted after removal of the solvent under reduced pressure.

**IV.3.10.1. Preparation of methyl (Z)-3-oxocyclopent-1-ene carboxylate (74):**

HOAc (35 mL), CrO$_3$ (13.5 mmol in 70 mL HOAc), DCM (250 mL) and unsaturated ester 73 (10 g, 79.4 mmol) were reacted and then quenched with KOH (12.5M, 50 mL) to produce 4 g (36%) of methyl (Z)-3-oxocyclopent-1-ene carboxylate 74 after SiO$_2$ flash chromatography (3:1 Hex:EtOAc as eluent) as a colourless oil.

**IV.3.10.2. Preparation of methyl (Z)-3-oxocyclohept-1-ene carboxylate (75):**

HOAc (3.5 mL), CrO$_3$ (13.5 mmol in 7 mL HOAc), DCM (25 mL) and unsaturated ester 64 (0.15 g, 1.0 mmol) were reacted and then quenched with KOH (12.5M, 5 mL) to produce 0.02 g (14%) of methyl (Z)-3-oxocyclohepta-1-ene carboxylate 75 after SiO$_2$ flash chromatography (10:1 Hex:EtOAc as eluent) as a colourless oil.

**IV.3.11. General procedure used for preparation of keto-esters (27), (28) and (24) using dirhodium (II) catalyst:**

![Chemical structures and reaction scheme](image-url)
A mixture of unsaturated ester, TBHP (5 eq) and Rh$_2$(cap)$_4$ (0.5 mol%) in DCM was stirred and heated at 50 °C. After 24 h a second portion of Rh$_2$(cap)$_4$ (0.5 mol%) and TBHP (5 eq) were added and the reaction mixture left to stir and heat at 50 °C for an additional 48 h. Crude keto-ester resulted after removal of the solvent under reduced pressure.

**IV.3.11.1. Preparation of methyl (Z)-3-oxocyclopent-1-ene carboxylate (74):**

Unsaturated ester 73 (7.1 g, 56 mmol), TBHP (281 mmol, 3 eq.) and Rh$_2$(cap)$_4$ (0.03 mmol, 0.5 mol%) in DCM (80 mL) produced 2.9 g (37%) of methyl (Z)-3-oxocyclopent-1-ene carboxylate 74 after SiO$_2$ flash chromatography (3:1 Hex:EtOAc as eluent) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.68 (t, $J$=2.1 Hz, 1H), 3.81 (s, 3H), 2.77-2.81 (m, 2H), 2.50-2.44 (m, 2H).

$^{13}$C NMR (400 MHz, CDCl$_3$): δ 209, 164.7, 163.8, 138.1, 52.5, 35.5, 27.4.

FT-IR (cm$^{-1}$, Neat): 2955, 2926, 1720, 1611, 1434, 1254, 1223, 1165.

**IV.3.11.2. Preparation of methyl (Z)-3-oxocyclohept-1-ene carboxylate (75):**

Unsaturated ester 64 (300 mg, 1.9 mmol) TBHP (5.8 mmol, 3 eq.) and Rh$_2$(cap)$_4$ (0.003 mmol, 0.5 mol%) in DCM (8 mL) produced 22 mg (30%) of methyl (Z)-3-oxocyclohept-1-ene carboxylate 75 after SiO$_2$ flash chromatography (10:1 Hex:EtOAc as eluent) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.8 (s, 1H), 3.77 (s, 3H), 2.59-27 (m, 4H), 1.86-174 (m, 4H).
$^{13}$C NMR (400 MHz, CDCl$_3$): δ 204.2, 168.0, 144.5, 137.1, 52.6, 42.6, 27.6, 24.9, 21.4.

FT-IR (cm$^{-1}$, Neat): 2951, 2868, 1721, 1674, 1437, 1248, 1195.

**IV.3.11.3. Preparation of methyl (Z)-3-oxycyclonona-1-enercarboxylate (76):**

After flash chromatography on a column of silica gel (15:1 Hex:EtOAc as eluent), unsaturated ester 65 (200 mg, 1.1 mmol) produced 7% of methyl (Z)-3-oxycyclonona-1-enercarboxylate 76 when 0.1 mol% of Rh$_2$(cap)$_4$, 5 eq of TBHP and 0.5 of K$_2$CO$_3$ were used. However, this reaction produced only 2% of 76 with the use of 2 mol% of Rh$_2$(cap)$_4$ and 5 eq of TBHP.

**IV.3.12. General procedure used for preparation of keto-acids (37), (38) and (39):**

A solution of K$_2$CO$_3$ (4 eq) in water was added to a stirred mixture of keto-ester in MeOH at room temperature. The reaction mixture was monitored using thin-layer chromatography and the reaction was completed after approximately six hours. Then 1 M HCl was added to acidify the reaction mixture and the solution was extracted with
Et₂O (50 mL × 3). The combined organic layer was washed with brine (80 mL), dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure to yield crude keto-acid.

**IV.3.12.1. Preparation of (Z)-3-oxocyclopent-1-ene carboxylic acid (37):**

Keto-ester 74 (2.9 g, 20.5 mmol) produced 1.6 g (62%) of (Z)-3-oxocyclopent-1-ene carboxylic acid 37 following recrystallization from isopropanol (20 mL).

**MP:**
193-194 °C

**¹H NMR (400 MHz, CD₃CN):**
δ 6.66 (t, J=2.2 Hz, 1H), 2.90-2.73 (m, 2H), 2.56-2.41 (m, 2H).

**¹³C NMR (400 MHz, CD₃CN):**
δ 209.2, 164.8, 164.5, 137.6, 35.3, 27.3.

**FT-IR (cm⁻¹, Nujol):**
3391, 1719, 1665, 1604, 1384, 1211.

**IV.3.12.2. Preparation of (Z)-3-oxocyclopeht-1-ene carboxylic acid (38):**

Keto-ester 75 (0.95 g, 5.61 mmol) produced 0.6 g (67%) of (Z)-3-oxocyclohept-1-ene carboxylic acid 38 as a yellow-oil that was of sufficient purity to use directly in the next step of the process.

**¹H NMR (400 MHz, CDCl₃):**
δ 6.93 (s, 1H), 2.60-2.67 (m, 4H), 1.86-1.72 (m, 4H).

**¹³C NMR (400 MHz, CDCl₃):**
δ 204.7, 172.1, 144.2, 138.4, 42.6, 27.3, 24.9, 21.6.

**FT-IR (cm⁻¹, Neat):**
3493, 2938, 2870, 1716, 1670, 1246, 1188.
**IV.3.12.3. Preparation of (Z)-3-oxocyclonona-1-ene carboxylic acid (39):**

Keto-ester 76 (0.9 g, 3.97 mmol) produced 0.6 g (86%) of (Z)-3-oxocyclonona-1-ene carboxylic acid 39 as a beige solid of sufficient purity to use directly in the next step of the process without any purification.

**IV.4. General procedure used for preparation of Diels-Alder reaction precursors (41), (42), (43) and (44):**

Under an inert argon atmosphere, keto-acid was dissolved in DCM, with oxalyl chloride (1 eq) and dimethylformamide (0.1 eq) added successively to the reaction mixture. After stirring and heating at reflux for 1 h the solvent was removed, and the formation of acid chloride checked using $^{13}$C NMR. The resulting acid chloride was dissolved in DCM, then Hunig’s base (1.5 eq) and diene-amine 36 (1 eq) were added to the reaction mixture, which was left to stir at rt overnight. The reaction mixture was washed with NaOH (10%), HCl (1M), H$_2$O and brine. The mixture was then dried over
MgSO\textsubscript{4} and filtered. Removal of the solvent under reduced pressure followed by purification via SiO\textsubscript{2} flash chromatography generated the amides 41-44.

**IV.4.1. Preparation of Diels-Alder reaction precursor (41):**

Unsaturated acid 37 (0.22 g, 1.7 mmol), oxalyl chloride (0.9 mL, 1.7 mmol) and diene-amine 36 (0.3 g, 1.7 mmol) in DCM (50 mL) produced 0.05 g (11%) of amide 41 after SiO\textsubscript{2} flash chromatography (1:1 Hex:EtOAc as eluent) as a colourless oil.

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}):} \( \delta \) 7.43-7.02 (m, 5H), 6.38-5.94 (m, 3H), 5.69-5.41 (m, 1H), 5.13 (dd, \( J = 17.0 \), 5.5 Hz, 1H), 5.08-4.99 (m, 1H), 4.71 (s, 1H), 4.50 (s, 1H), 3.52 (t, \( J = 7.2 \) Hz, 1H), 2.81 (dt, \( J = 6.9 \), 2.0 Hz, 1H), 2.61-2.18 (m, 4H).

\textbf{\textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}):} \( \delta \) 208.5, 169.3, 136.6, 134.2, 133.5, 130.7, 130.4, 129.1, 128.1, 126.6, 117.2, 116.2, 52.0, 47.1, 44.3, 34.4, 30.0.

\textbf{FT-IR (cm\textsuperscript{-1}, Neat):} 3064, 2927, 2871, 1714, 1632, 1605, 1449, 1437, 1229, 1172, 736, 703.

**IV.4.2. Preparation of Diels-Alder reaction precursor (42):**

Unsaturated acid 38 (0.45 g, 2.7 mmol), oxalyl chloride (1.3 mL, 2.7 mmol) reacted for 7 h in DCM (40 mL), then diene-amine 36 (0.5 g, 2.7 mmol) in DCM (60 mL) was added to produce 0.54 g (65%) of amide 42 after SiO\textsubscript{2} flash chromatography (2:1 Hex:EtOAc as eluent) as a colourless oil.
IV.4.3. Preparation of Diels-Alder reaction precursor (43):

Unsaturated acid 39 (0.4 g, 2.2 mmol), oxalyl chloride (1 mL, 2.2 mmol) and diene-amine 36 (0.41 g, 2.2 mmol) in DCM (90 mL) produced 0.75 g (87%) of amide 43 after SiO\textsubscript{2} flash chromatography (3:1 Hex:EtOAc as eluent) as a colourless oil.
**FT-IR (cm\(^{-1}\), Neat):**

3062, 2929, 2859, 1636, 1494, 1447, 1425, 734, 700.

**IV.4.4. Preparation of Diels-Alder reaction precursor (44):**

Unsaturated acid 40 (1.5 g, 7.1 mmol), oxalyl chloride (3.6 mL, 7.1 mmol) and diene-amine 36 (1.3 g, 7.1 mmol) in DCM (130 mL) produced 1.75 g (65%) of amide 44 after SiO\(_2\) flash chromatography (5:1 Hex:EtOAc as eluent) as a colourless oil.

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):**

\[\delta 7.39-7.07 \text{ (m, 5H)}, 6.34-6.14 \text{ (m, 2H)}, 6.11-5.93 \text{ (m, 1H)}, 5.67-5.42 \text{ (m, 1H)}, 5.08 \text{ (d, } J = 17.0 \text{ Hz, 1H)}, 4.98 \text{ (d, } J = 9.9 \text{ Hz, 1H)}, 4.59 \text{ (s, 1H)}, 4.48 \text{ (s, 1H)}, 3.38 \text{ (s, 1 H)}, 3.16 \text{ (s, 1H)}, 2.83-2.60 \text{ (m, 2H)}, 2.47-2.20 \text{ (m, 4H)}, 1.83-1.17 \text{ (m, 12).}

**\(^{13}\)C NMR (400 MHz, CDCl\(_3\)):**

\[\delta 205.6, 170.8, 148.9, 136.7, 133.7, 133.2, 130.8, 130.0, 128.8, 127.9, 126.7, 116.6, 115.8, 51.6, 45.6, 44.1, 43.0, 30.3, 27.2, 25.3, 25.1, 25.0, 23.48.

**FT-IR (cm\(^{-1}\), Neat):**

3067, 2933, 2867, 1686, 1633, 1492, 1466, 1451, 1425, 734.
**IV.4.5. Mixed anhydride procedure used for preparation of Diels-Alder reaction precursor (41):**

Under an inert argon atmosphere, N-methylmorphline (0.9 mL, 7.9 mmol) was added slowly to a cold solution (-5 to -10 °C) of keto-acid 37 (1 g, 7.9 mmol) and isobutychloroformate (98 %, 1 mL, 7.9 mmol) in DCM (200 mL). The reaction mixture was allowed to stir for 30 minutes at -5 to -10 °C, and then cold diene-amine 36 (1.5 g, 7.9 mmol) in DCM (10 mL) was added slowly. This mixture was left to stir at the same temperature for one hour, and then at rt overnight. The reaction mixture was quenched with an aqueous saturated solution of citric acid (70 mL) and the layers were separated. The aqueous phase was extracted with DCM (40 mL × 3) and the combined organic phase was washed with aqueous saturated solution of NaHCO₃ (50 mL), dried over MgSO₄ and filtered. After removing the solvent under reduced pressure, flash chromatography (1:1 Hex:EtOAc as eluent) produced 1.3 g (57 %) of Diels-Alder reaction precursor 41.
**IV.5. General procedure for the Diels-Alder reactions:**

A solution of Diels-Alder reaction precursor in toluene was degassed by bubbling argon through it for 30 minutes. The solution, under an inert argon atmosphere, was then stirred and heated at reflux for the indicated time. Upon cooling to rt the solvent was removed under reduced pressure and the residue was subjected to SiO₂ flash chromatography to generate pure endo and exo products.

**IV.5.1. Preparation of endo product (45) and exo product (46):**

Amide 41 (0.65 g, 2.2 mmol) heated in toluene (50 mL) for 120 h produced 0.2 g (31%) of endo cycloadduct 45 as white solid and 0.1 g (16 %) of exo cycloadduct 46 as a yellow oil after SiO₂ flash chromatography (1:1 Hex:EtOAc as eluent). This ratio of 2:1 endo:exo was the same observed in the crude ¹H NMR obtained immediately after evaporation of solvent.
Endo (45)

MP: 104-105 °C

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.36-7.07 (m, 5H), 5.79 (ddt, $J = 9.9$, 4.9, 2.7 Hz, 1H), 5.37 (dd, $J = 10.2$, 2.1 Hz, 1H), 4.67 (d, $J = 14.8$ Hz, 1H), 4.49 (d, $J = 14.8$ Hz, 1H), 3.31 (d, $J = 7.8$ Hz, 1H), 3.22 (td, $J = 12.6$, 3.9 Hz, 1H), 3.10-3.00 (m, 1H), 2.61-2.43 (m, 2H), 2.37-1.99 (m, 6H), 1.68 (ddd, $J = 13.7$, 5.5, 3.7 Hz, 1H).

$^{13}$C NMR (400 MHz, CDCl$_3$): δ 216.0, 172.3, 137.0, 129.0, 128.6, 127.5, 127.3, 127.1, 52.3, 51.1, 47.5, 43.8, 33.6, 31.7, 30.7, 24.8, 20.2.

FT-IR (cm$^{-1}$, Neat): 3023, 2931, 2869, 1741, 1629, 1494, 1453, 1358, 1270, 1252, 1206, 735, 700.

Exo (46)

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.38-7.15 (m, 5H), 5.76 (ddt, $J = 9.6$, 5.1, 3.2 Hz, 1H), 5.52 (dt, $J = 9.6$, 2.6, 1.1 Hz, 1H), 4.72 (d, $J = 14.5$ Hz, 1H), 4.28 (d, $J = 14.5$ Hz, 1H), 3.31-3.24 (m, 2H), 2.86 (dd, $J = 10.0$, 5.4 Hz, 1H), 2.56-2.41 (m, 2H), 2.34-2.19 (m, 2H), 2.18-2.07 (m, 1H), 2.01-1.8 (m, 4H).

$^{13}$C NMR (400 MHz, CDCl$_3$): δ 218.4, 174.9, 137.3, 129.4, 128.7, 128.1, 127.4, 127.3, 50.0, 49.3, 47.7, 46.1, 35.1, 34.5, 28.1, 24.6, 23.4.
IV.5.2. Preparation of endo product (47) and exo product (48):

A mixture of amide 42 (0.283g, 0.088 mmol) in toluene (5 mL) heated in a sealed tube for 288 h produced 59 mg (21%) of endo cycloadduct 47 and 30 mg (11 %) of exo cycloadduct 48 after SiO₂ flash chromatography (1:1 Hex:EtOAc as eluent) as colourless oils. This ratio of 2:1 endo:exo was the same observed in the crude ¹H NMR obtained immediately after evaporation of solvent.

Endo (47)

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.09 (m, 5H), 5.87 (dq, J = 7.6, 2.5 Hz, 1H), 5.52-5.36 (m, 1H), 4.58 (d, J = 14.8 Hz, 1H), 4.46 (d, J = 14.7 Hz, 1H), 3.80 (d, J = 5.0 Hz, 1H), 3.15 (td, J = 12.4, 5.1 Hz, 1H), 3.05 (dd, J = 11.8, 5.8 Hz, 1H), 2.70-2.60 (m, 1H), 2.47-2.37 (m, 1H), 2.37-2.19 (m, 3H), 2.19-2.00 (m, 2H), 1.98-1.78 (m, 2H), 1.72-1.55 (m, 4H).

¹³C NMR (400 MHz, CDCl₃): δ 214.05, 173.47, 137.34, 128.79, 128.48, 128.45, 127.63, 127.16, 127.02, 50.78, 48.81, 44.47, 44.28, 43.71, 38.85, 35.39, 29.69, 25.05, 23.51, 23.22, 22.06.

FT-IR (cm⁻¹, Neat): 3027, 2938, 2880, 1741, 1494, 1452, 1266, 1166, 735, 702.
Exo (48)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41-7.10 (m, 5H), 5.73-5.61 (m, 1H), 5.38 (dd, $J = 9.7, 2.0$ Hz, 1H), 4.88 (d, $J = 14.7$ Hz, 1H), 4.19 (d, $J = 14.7$ Hz, 1H), 3.37-3.10 (m, 2H), 3.11-2.87 (m, 2H), 2.71-2.57 (m, 2H), 2.58-2.20 (m, 2H), 2.00-1.58 (m, 8H).

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 214.2, 173.2, 137.4, 128.6, 128.48, 128.03, 128.0, 127.95, 127.7, 125.3, 58.2, 50.8, 50.1, 45.1, 43.1, 40.2, 27.7, 27.0, 25.5, 24.2, 23.2.

FT-IR (cm$^{-1}$, Neat): 3025, 2920, 2861, 1684, 1636, 1495, 1452, 1249, 1185, 1077, 727, 700.

VI.5.3. Preparation of endo product (49) and exo product (50):

Amide 43 (0.7 g, 2.1 mmol) heated in toluene (50 mL) for 192 h produced 0.27 g (39%) of endo cycloadduct 49 as a colorless oil and 0.02 g (2 %) of exo cycloadduct 50 as yellow oils after SiO$_2$ flash chromatography (2:1 Hex:EtOAc as eluent). This ratio of 18:1 endo:exo was the same observed in the crude $^1$H NMR spectrum obtained immediately after evaporation of solvent.

Endo (49)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38-7.06 (m, 5H), 5.69 (ddt, $J = 9.8, 4.8, 2.3$ Hz, 1H), 5.58 (ddt, $J = 10.1, 2.9, 1.6$ Hz, 1H), 4.48 (q, $J = 14.3$ Hz, 2H), 4.12 (d, $J = 7.2$ Hz, 1H), 3.19-3.09 (m, 1H), 3.05-2.97 (m, 1H), 2.91 (s, 1H), 2.71 (ddd, $J = 12.7, 3.5$ Hz, 2H), 2.29-1.20 (m, 14H).
\[ ^{13}C \text{ NMR (400 MHz, CDCl}_3): \delta 217.3, 172.9, 137.5, 129.5, 128.4, 127.5, 127.1, \\
126.0, 50.7, 47.0, 45.4, 44.4, 41.47, 34.3, 33.0, \\
27.0, 25.5, 23.8, 23.2, 22.0, 18.1. \]

\[ \text{FT-IR (cm}^{-1}, \text{ Neat):} \]
3023, 2931, 1701, 1628, 1494, 1475, 1453, 1354, \\
1193, 734, 701.

**Exo (50)**

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_3): \delta 7.35-7.22 \text{ (m, 5H), } 6.05 \text{ (ddt, } J = 9.0, 6.2, 3.1 \text{ Hz,} \\
1\text{H), } 5.56 \text{ (dt, } J = 9.0, 3.1 \text{ Hz, } 1\text{H), } 4.75 \text{ (d, } J = \\
14.5 \text{ Hz, } 1\text{H), } 4.40 \text{ (d, } J = 14.5 \text{ Hz, } 1\text{H), } 3.66 \text{ (dd, } J \\
= 7.7, 3.9, \text{ Hz, } 1\text{H), } 3.47-3.17 \text{ (m, 2H), } 3.01 \text{ (ddd, } J \\
= 15.3, 10.6, 3.2 \text{ Hz, } 1\text{H), } 2.79-2.66 \text{ (m, } 1\text{H), } 2.50-
2.32 \text{ (m, } 3\text{H), } 2.14-1.16 \text{ (m, } 12\text{H).} \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3): \delta 215.2, 174.8, 137.5, 130.3, 129.0, 128.6, 128.3, \\
127.4, 54.4, 50.7, 50.7, 44.5, 40.5, 39.0, 26.9, 26.4, \\
25.3, 25.1, 23.9, 22.9, 22.8. \]

\[ \text{FT-IR (cm}^{-1}, \text{ Neat):} \]
3028, 2925, 2854, 1698, 1635, 1495, 1446, 1264, \\
1224, 1020, 734, 701.

**VI.5.4. Preparation of endo product (51) and exo product (52):**

Amide 44 (1.6 g, 4.2 mmol) heated in toluene (100 mL) for 192 h produced 0.9 g (54%) of endo cycloadduct 51 as a white solid and 0.2 g (10 %) of exo cycloadduct 52 as a colorless oil after SiO\(_2\) flash chromatography (3:1 Hex:EtOAc as eluent). This ratio of 5.4:1 endo:exo was the same observed in the crude \(^1\)H NMR spectrum obtained immediately after evaporation of solvent.
Endo (51)

**MP:** 122-124 °C

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):**
\[\delta 7.38-7.06 \text{ (m, 5H)}, 5.63 \text{ (ddt, } J = 9.6, 4.7, 2.0 \text{ Hz, 1H)}, 5.56 \text{ (d, } J = 10.2 \text{ Hz, 1H)}, 4.54 \text{ (d, } J = 14.7 \text{ Hz, 1H)}, 4.43 \text{ (d, } J = 14.7 \text{ Hz, 1H)}, 4.02 \text{ (d, } J = 7.7 \text{ Hz, 1H)}, 3.19 \text{ (s, 1H)}, 3.16-2.97 \text{ (m, 2H)}, 2.61 \text{ (ddd, } J = 14.7, 9.5, 1.6 \text{ Hz, 1H)}, 2.37 \text{ (ddtd, } J = 16.4, 7.9, 4.3, 2.4 \text{ Hz, 1H)}, 2.30-2.13 \text{ (m, 2H)}, 2.08-1.82 \text{ (m, 2H)}, 1.81-1.10 \text{ (m, 14H)}.\]

**\(^{13}\)C NMR (400 MHz, CDCl\(_3\)):**
\[\delta 214.2, 172.4, 137.6, 130.3, 128.4, 127.6, 127.0, 125.0, 50.7, 47.3, 45.5, 44.3, 41.3, 35.4, 33.1, 26.9, 26.8, 25.4, 24.2, 23.3, 22.1, 21.9, 19.2.\]

**FT-IR (cm\(^{-1}\), Neat):**
3018, 2933, 2867, 1704, 1628, 1487, 1468, 1441, 732, 700.

Exo (52)

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):**
\[\delta 7.45-7.19 \text{ (m, 5H)}, 5.71 \text{ (dq, } J = 9.7, 3.2 \text{ Hz, 1H)}, 5.32 \text{ (dq, } J = 9.8, 2.0 \text{ Hz, 1H)}, 4.56 \text{ (q, } J = 18.8 \text{ Hz, 2H)}, 3.30-3.15 \text{ (m, 2H)}, 3.09 \text{ (td, } J = 12.5, 3.5 \text{ Hz, 1H)}, 2.77 \text{ (dd, } J = 10.7, 7.1 \text{ Hz, 1H)}, 2.55-2.31 \text{ (m, 3H)}, 2.29-2.03 \text{ (m, 2H)}, 2.03-1.11 \text{ (m, 15H)}.\]

**\(^{13}\)C NMR (400 MHz, CDCl\(_3\)):**
\[\delta 214.9, 172.8, 137.0, 128.5, 128.4, 127.9, 127.3, 127.3, 557.3, 50.3, 46.2, 45.6, 40.8, 39.5, 29.3, 26.4, 26.2, 24.4, 23.6, 23.4, 22.6, 19.9, 19.7.\]
FT-IR (cm$^{-1}$, Neat): 3026, 3025, 2931, 2871, 1681, 1632, 1494, 1472, 1448, 734, 701.
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APPENDIX A: 1D-\(^1\)H NMR Spectra
O

On 75 n=3
$42n = 3$
Endo

$47 \ n = 3$
Exo 48 \( n = 3 \)


$43n = 5$
Exo $n = 5$
$72 \ n=7$
$40 \ n=7$
$44 \ n = 7$
Endo $n = 7$
APPENDIX B: 1D-$^{13}$C NMR Spectra
61 $n=1$
$\text{O} \quad n=3 \quad \text{O}$

$\text{O} \quad \text{C} \quad n=3 \quad \text{O}$
$75 \ n=3$
\[42n = 3\]
Endo 47 n = 3
Exo
48  n = 3
On 43, \( n = 5 \)
Endo

49 n = 5
n = 7
Endo

$51 \ n = 7$
Exo

52  n = 7
APPENDIX C: 2D- COSY NMR Spectra
APPENDIX D: 2D- HMBC NMR Spectra
\[ \text{Endo} \ 47 \ n = 3 \]
APPENDIX E: 2D- HSQC NMR Spectra
$^{13}$C NMR: $n = 3$

**Endo 47**
Exo 48 \( n = 3 \)
APPENDIX F: 2D- NOESY NMR Spectra
Endo $47 \ n = 3$
Exo

52  n = 7
APPENDIX G: IR Spectra
$n = 3$
$n = 3$

$42$ n = 3

Wavenumbers (cm$^{-1}$)

% Transmittance
Endo 47 n = 3
44 n = 7
Endo

51  n = 7
Curriculum Vitae

Candidate’s full name: Narjs Moslem Alnakhli

Universities attended:

- (2013-2015) University of New Brunswick, Chemistry Department, Master of Science
- (2014) University of New Brunswick, Diploma in University Teaching
- (2005-2009) Taibah University, Chemistry Department, B.Sc.